
Veterinary Neuropathology

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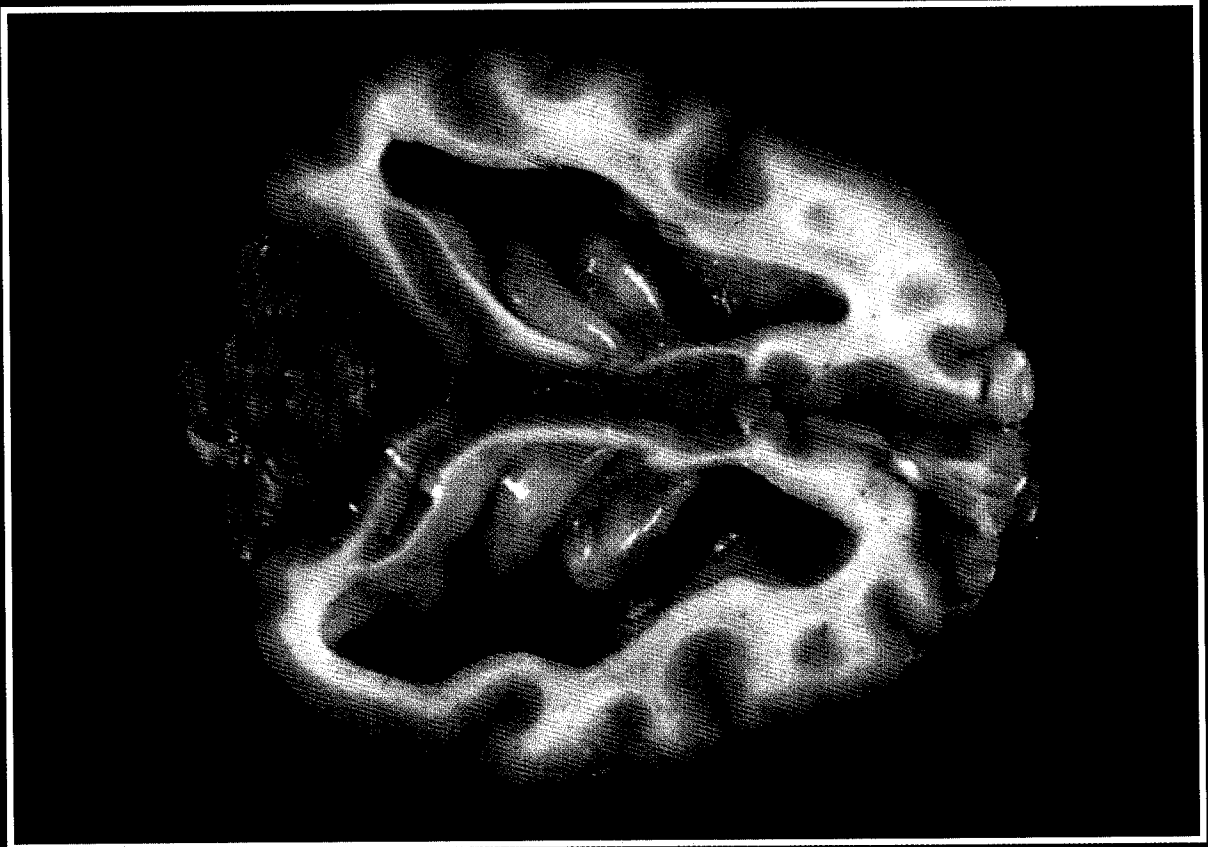
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with 564 illustrations

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CONTENTS

Chapter 1 Principles of Neuropathology, 1

- Introduction to the Central Nervous System, 1*
- Historical introduction, 1
- Embryology and anatomy: a synopsis, 1
- Cellular composition of the central nervous system, 2
- The language of neuropathology, 3
- Neurons, 4
- Astrocytes and oligodendrocytes, 10
- Ependyma and choroid plexus epithelium, 18
- Microglial cells and macrophages, 19
- Microvasculature, 23
- Immunobiology and immunopathology of the central nervous system, 23
- Approaching neuropathology, 25
- Examination of the Central Nervous System, 27*
- Introduction, 27
- Fixation for electron microscopy, 29
- Histochemistry and immunohistochemistry, 29
- Molecular biology, 30
- Tissue culture, 32
- Normal features and artifacts, 32
- Diseases without lesions, 35
- Cerebral Edema and Brain Swelling, 36*
- Inflammation of the Central Nervous System, 39*
- Hallmarks of CNS inflammation, 39
- Demyelination, 42
- Infectious agents and CNS inflammation, 44
- Neuroinvasiveness and neurovirulence, 46
- Ancillary Procedures in Neurological Disease, 47*
- Neuropathology of Aging, 49*
- Introduction, 49
- Neuronal and glial populations, 49
- White matter, 50
- Inclusions within cells, 51
- Leptomeninges, choroid plexus, and blood vessels, 52
- Alzheimer's disease and pathological comparisons in animals, 54

Chapter 2 Malformations of the Central Nervous System, 68

- Brain, 68*
- Cerebrum, 68
 - Cerebral aplasia, 68
 - Encephalocele, meningoencephalocele, meningocele, exencephaly, 69
 - Holoencephaly, arhinencephaly, cyclopia, 71
 - Agensis of the corpus callosum, 72
 - Hydranencephaly, porencephaly, 72
 - Lissencephaly, pachygyria, 73

| | |
|--|----|
| Polymicrogyria, | 74 |
| Microencephaly, | 74 |
| Megalecephaly, | 74 |
| Hydrocephalus, | 75 |
| Hydromyelia, syringomyelia, | 77 |
| Miscellaneous, | 78 |
| Brain stem, | 78 |
| Diencephalon, | 78 |
| Microphthalmia, anophthalmia, optic nerve hypoplasia, aplasia, | 78 |
| Mesencephalon, | 79 |
| Pons, | 79 |
| Medulla, | 79 |
| Arnold-Chiari malformation, | 79 |
| Cerebellum, | 82 |
| Viral infections, | 82 |
| Primary malformations, | 85 |
| Dandy-Walker syndrome, | 86 |
| <i>Spinal Cord,</i> | 86 |
| Meningocele, meningocele, | 86 |
| Diplomyelia, diastatomyelia, | 86 |
| Myelodysplasia, | 88 |
| Miscellaneous, | 90 |

Chapter 3 Inflammatory Diseases of the Central Nervous System, 95

| | |
|--|-----|
| Rabies, | 95 |
| Aujeszky's disease, | 99 |
| Canine distemper encephalomyelitis, | 102 |
| Granulomatous meningoencephalomyelitis, | 110 |
| Pug dog encephalitis, | 111 |
| Idiopathic immune-mediated polyarteritis and meningoencephalomyelitis, | 114 |
| Canine herpesvirus encephalomyelitis, | 117 |
| Canine adenovirus CNS vasculitis, | 117 |
| Parainfluenza and Newcastle disease encephalomyelitis, | 117 |
| Meningoencephalomyelitis in Pointer dogs, | 118 |
| Feline infectious peritonitis, | 119 |
| Feline polioencephalomyelitis, | 119 |
| Feline immunodeficiency virus encephalomyelitis, | 122 |
| Feline demyelinating optic neuritis, | 122 |
| Enterovirus encephalomyelitis, | 123 |
| Miscellaneous causes of porcine encephalomyelitis, | 125 |
| Caprine arthritis encephalitis syndrome, | 128 |
| Visna, | 129 |
| Louping ill, | 132 |
| Listeriosis, | 133 |
| Scrapie and the transmissible encephalopathies, | 136 |
| Bovine herpesvirus meningoencephalomyelitis, | 141 |
| Sporadic meningoencephalomyelitis of Swiss cattle, | 141 |
| Malignant catarrhal fever, | 142 |
| Thrombotic meningoencephalitis of cattle, | 143 |
| Sporadic bovine encephalomyelitis, | 144 |
| Equine viral encephalomyelitis, | 144 |
| Equine herpesvirus 1 encephalomyelopathy, | 146 |
| Equine infectious anemia, | 146 |
| Borna disease, | 148 |
| Murine coronavirus encephalomyelitis, | 149 |

- Miscellaneous CNS infections, 150
- Meningitis and brain abscesses, 156
- Parasitic encephalomyelitis, 159
- Protozoan encephalomyelitis, 162

Chapter 4 Injuries to the Central Nervous System, 189

- Traumatic injury to the central nervous system, 189
- Vertebral malformations and spinal cord injury, 193
- Intervertebral disk disease and spinal cord injury, 202
- Post-traumatic blindness and optic nerve degeneration in the horse, 204
- Calcinosis circumscripta and spinal cord compression, 204

Chapter 5 Degenerative Diseases of the Central Nervous System, 208

- Metabolic and Circulatory Disorders, 208*
- Hepatic and renal encephalopathy, 208
- Disorders of intermediary metabolism, 211
- Lysosomal storage diseases, 214
- Central nervous system hypoxia, ischemia, and related disorders, 237
- Intoxications and Toxicoinfectious Diseases, 250*
- Lead poisoning, 250
- Arsenic poisoning, 252
- Mercury poisoning, 253
- Salt poisoning, 254
- Delayed organophosphate poisoning, 255
- Chlorinated hydrocarbon insecticide poisoning, 256
- Ethylene glycol poisoning, 257
- Hexachlorophene poisoning, 258
- Levamisole, 258
- Selenium poisoning and focal symmetrical poliomyelomalacia, 258
- Tremorgenic syndromes, 261
- Equine nigropallidal encephalomalacia, 263
- Solanum poisoning in cattle, 264
- Cycad poisoning, 264
- Miscellaneous poisons, 265
- Edema disease, 267
- Focal symmetrical encephalomalacia, 269
- Equine leukoencephalomalacia, 270
- Nutritional Diseases, 271*
- Vitamin A deficiency, 271
- Vitamin E deficiency, 272
- Copper deficiency: swayback and enzootic ataxia, 273
- Thiamine deficiency and polioencephalomalacia, 277
- Hereditary, Familial, and Idiopathic Degenerative Diseases, 281*
- Leukodystrophies, hypomyelination, spongy degeneration, and related disorders, 281
- Neuronal abiotrophy, 300
- Motor neuron diseases, 307
- Neuroaxonal dystrophy, 315
- Equine degenerative myeloencephalopathy, 317
- Degenerative myelopathy of old animals, 319
- Hound ataxia, 321
- Ataxia and myelopathy in Terrier dogs, 321
- Nervous system degeneration in the Ibizan hound, 322
- Labrador Retriever axonopathy, 323
- Myelopathy in Kooiker dogs, 324
- Myelopathy in Merino sheep, 324

- Progressive degenerative myeloencephalopathy of Brown Swiss cattle (weaver syndrome), 325
- Progressive spinal myelinopathy in Murray Grey cattle, 325
- Congenital axonopathy in Holstein-Friesian calves, 325
- Encephalomyelopathy in Simmental and Limousin calves, 326
- Neuronal glycoproteinosis, 326
- Miscellaneous bovine encephalopathies, 327

Chapter 6 Tumors of the Central Nervous System, 351

- Introduction, 351
- Malformations, hamartomas, cysts, and borderline tumors, 352
- Meningeal tumors, 355
- Astroglial tumors, 362
- Oligodendroglial tumors, 370
- Choroid plexus tumors, 373
- Ependymal tumors, 375
- Neuronal tumors, 375
- Medulloblastomas and primitive neuroectodermal tumors, 378
- Pineal tumors, 379
- Miscellaneous central nervous system tumors, 379
- Central nervous system-associated tumors, 380
- Metastatic central nervous system tumors, 391

Chapter 7 Diseases of the Peripheral Nervous System, 402

- Introduction and General Pathology of the Peripheral Nervous System, 402*
- Introduction, 402
- General pathology of the peripheral nervous system, 414
- Common artifacts in the peripheral nervous system, 422
- Inflammatory Diseases of the Peripheral Nervous System, 424*
- Acute idiopathic polyradiculoneuritis, 424
- Chronic polyradiculoneuritis, 427
- Brachial plexus neuritis, 427
- Canine ganglioradiculitis (sensory neuropathy), 428
- Enteric ganglionitis, 431
- Neuritis of the cauda equina, 433
- Protozoan polyradiculoneuritis, 434
- Granulomatous radiculitis of the seventh and eighth cranial nerves in calves, 436
- Cranial neuritis with guttural pouch mycosis and empyema in the horse, 436
- Degenerative Diseases of the Peripheral Nervous System, 437*
- Canine inherited hypertrophic neuropathy, 437
- Hypertrophic polyneuropathy in the cat, 439
- Focal trigeminal hypertrophic neuropathy in a horse, 440
- Congenital hypomyelinating polyneuropathy in Golden Retrievers, 441
- Hereditary polyneuropathy in Alaskan Malamutes, 441
- Hereditary sensory neuropathy in Pointer dogs, 442
- Sensory neuropathy in longhaired Dachshunds, 443
- Canine giant axonal neuropathy, 444
- Progressive axonopathy of Boxer dogs, 445
- Polyneuropathy in Rottweiler dogs, 445
- Epizootic peroneal and tibial neuropathy in unweaned Walker Hound pups, 446
- Peripheral neuropathy in German Shepherd dogs, 446
- Distal denervating disease, 447
- Dancing Doberman disease, 447
- Peripheral neuropathy in twin calves, 447
- Idiopathic facial paralysis in the dog and cat, 448
- Equine laryngeal hemiplegia, 448

| | |
|---|-----|
| Canine laryngeal paralysis, | 450 |
| Stringhalt, | 451 |
| Leukoencephalomyeloneuropathy in Birman cats, | 452 |
| Kangaroo gait in ewes, | 452 |
| Feline ischemic neuromyopathy, | 453 |
| <i>Traumatic Lesions of the Peripheral Nervous System,</i> | 453 |
| Avulsions of the brachial plexus, | 453 |
| Cauda equina syndrome, | 454 |
| Injection injuries to peripheral nerves, | 455 |
| Amputation neuroma, | 455 |
| Calving paralysis and downer cows, | 457 |
| Femoral nerve paralysis in calves and horses, | 457 |
| Entrapment of the suprascapular nerve in horses, | 458 |
| <i>Metabolic and Nutritional Disorders Affecting the Peripheral Nervous System,</i> | 458 |
| Globoid cell leukodystrophy, | 458 |
| Canine α -1-fucosidosis, | 459 |
| Caprine and feline mannosidosis, | 460 |
| Feline Niemann-Pick disease polyneuropathy, | 460 |
| Atypical canine GM ₂ gangliosidosis with muscle weakness and wasting, | 461 |
| Diabetic neuropathy, | 462 |
| Hypothyroid neuropathy, | 462 |
| Pantothenic acid deficiency in swine, | 463 |
| Riboflavin deficiency in chickens, | 463 |
| Inherited neuroaxonal dystrophy in C ₆ -deficient rabbits, | 464 |
| Neuropathy associated with inherited hyperchylomicronemia in cats, | 464 |
| Neuropathy associated with primary hyperoxaluria in cats, | 465 |
| <i>Poisoning and the Peripheral Nervous System,</i> | 465 |
| Lead poisoning, | 465 |
| Thallium poisoning, | 466 |
| Mercury poisoning, | 466 |
| Pyridoxine poisoning, | 467 |
| Vincristine neuropathy, | 468 |
| Mycotoxic peripheral myelinopathy, | 468 |
| Coyotillo (buckthorn) polyneuropathy, | 469 |
| <i>Autonomic Nervous System,</i> | 469 |
| Disorders of the autonomic nervous system, | 469 |
| <i>Neoplasia and the Peripheral Nervous System,</i> | 472 |
| Paraneoplastic neuropathy, | 472 |
| Neuropathy associated with insulinoma, | 472 |
| Tumors of the peripheral nervous system, | 473 |

Appendix 1 Abbreviations, 502

Appendix 2 Terminology, 503

Appendix 1 ABBREVIATIONS

| | | | |
|-------|--|-------|---|
| ACTH | Adrenocorticotrophic hormone | ISMA | Infantile spinal muscular atrophy |
| AIDS | Acquired immunodeficiency syndrome | LFB | Luxol fast blue |
| ALS | Amyotrophic lateral sclerosis | LM | Light microscopy |
| ASF | African swine fever | LMN | Lower motor neuron |
| BBB | Blood-brain barrier | MAG | Myelin associated glycoprotein |
| BD | Border disease | MBP | Myelin basic protein |
| BHV | Bovine herpesvirus | MCB | Membranous cytoplasmic body |
| BSE | Bovine spongiform encephalopathy | MFD | Minimum flexion diameter |
| BVD | Bovine virus diarrhea | MHC | Major histocompatibility complex |
| CAES | Caprine arthritis encephalitis syndrome | MLD | Metachromatic leukodystrophy |
| CAT | Computerized axial tomography | MPNST | Malignant peripheral nerve sheath tumor |
| CCN | Cerebrocortical necrosis | MPS | Mucopolysaccharidosis |
| CD | Canine distemper | MRI | Magnetic resonance imaging |
| CDE | Canine distemper encephalomyelitis | MSD | Minimum sagittal diameter |
| CHP | Coonhound paralysis | MuLV | Murine leukemia virus |
| CHV | Canine herpesvirus | NAD | Neuroaxonal dystrophy |
| CNS | Central nervous system | NCAM | Neural cell adhesion molecule |
| CPIV | Canine parainfluenza virus | NCE | Neuritis of the cauda equina |
| CSF | Cerebrospinal fluid | NF 1 | Neurofibromatosis type 1 |
| CSM | Cervical stenotic myelopathy | NK | Natural killer (cells) |
| CVMM | Cervical vertebral malformation-malarticulation | NMS | Neonatal maladjustment syndrome |
| EDM | Equine degenerative myeloencephalopathy | NSE | Neuron-specific enolase |
| EE | Eastern encephalomyelitis | OAAM | Occipitoatlantoaxial malformation |
| EEG | Electroencephalography | PAS | Periodic acid Schiff |
| EIA | Equine infectious anemia | PCR | Polymerase chain reaction |
| EM | Electron microscopy | PDGF | Platelet derived growth factor |
| EMC | Encephalomyocarditis (virus) | PEM | Polioencephalomalacia |
| EMG | Electromyography | PLP | Proteolipid protein |
| EPM | Equine protozoal myelitis (or myeloencephalitis) | PNET | Primitive neuroectodermal tumor |
| FCEM | Fibrocartilaginous embolic myelopathy | PNS | Peripheral nervous system |
| FIP | Feline infectious peritonitis | PrP | Prion protein |
| FIV | Feline immunodeficiency virus | PTAH | Phosphotungstic acid hematoxylin |
| FSE | Focal symmetrical encephalomalacia | rER | Rough endoplasmic reticulum |
| GABA | Gamma aminobutyric acid | RMSF | Rocky mountain spotted fever |
| GC | Galactocerebroside | SAF | Scrapie associated fibrils |
| GCL | Globoid cell leukodystrophy | sER | Smooth endoplasmic reticulum |
| GFAP | Glial fibrillary acidic protein | SIP | Scrapie incubation period |
| GME | Granulomatous meningoencephalomyelitis | SLE | Systemic lupus erythematosus |
| GP | General proprioception | SP | Substance P |
| H&E | Hematoxylin and eosin | SVD | Swine vesicular disease |
| HC | Hog cholera | TME | Thrombotic meningoencephalitis |
| HE | Hepatic encephalopathy | TNF | Tumor necrosis factor |
| HEV | Hemagglutinating encephalomyelitis virus | TrME | Transmissible mink encephalopathy |
| HIV | Human immunodeficiency virus | UMN | Upper motor neuron |
| HMSN | Hereditary motor and sensory neuropathy | VE | Venezuelan encephalomyelitis |
| HPNSD | Hereditary porcine neuronal system degeneration | VIP | Vasoactive intestinal peptide |
| IF | Interferon | VWD | Vomiting and wasting disease |
| IL | Interleukin | WE | Western encephalomyelitis |

Chapter 1 PRINCIPLES OF NEUROPATHOLOGY

Introduction to the central nervous system

Historical introduction
Embryology and anatomy: a synopsis
Cellular composition of the central nervous system
The language of neuropathology
Neurons
Astrocytes and oligodendrocytes
Ependyma and choroid plexus epithelium
Microglial cells and macrophages
Microvasculature
Immunobiology and immunopathology of the central nervous system
Approaching neuropathology

HISTORICAL INTRODUCTION

Although neurological disorders in animals were recognized from at least the seventeenth century,¹ veterinary neuropathology has but a brief history. By the late nineteenth century, the neurosciences were a well-developed field in human medicine, and some of the earliest neuropathological studies in animals were conducted by physicians, as when Gowers (with Sankey) reported on canine distemper myelitis in 1877. Few veterinarians attempted to systematically study neurological disorders at that time. Dexler² published a volume on the neurological disorders of the horse in 1899, but in the true sense of the word he was exceptional.

Many of the early veterinary exponents of animal neurology and pathology obtained their formal training from colleagues in human medicine. In some centers, a long-standing collaboration was established, notably that between Fankhauser and Frauchiger in Switzerland. In one form or another, this interaction continues and is to be encouraged. The professional associations of neuropathologists in many countries have both physicians and veterinarians in their ranks.

The consolidation of veterinary neurology and neuropathology can be traced back to the post-World War II period. A link soon emerged between veterinary neurology and neuropathology that was a marriage of necessity. Clinical neurologists quickly recognized their dependence on high-quality pathological studies if their knowledge and understanding were to advance. In the absence of trained veterinary neuropathologists, many taught themselves in this discipline. Clinical assistance arrived with the publication of Frauchiger and Fankhauser's *Neurological Diseases of the Dog* in 1949 and McGrath's *Neurological Examination of the Dog* in 1956. Nine years later, Palmer published *Introduction to Animal Neurology*, and Hoerlein's *Canine Neurology, Diagnosis, and Treatment* became available. Landmark contributions in veterinary neuropathology were Frauchiger and Fankhauser's *Comparative Neuropathology of Man and Animals* in 1957, Innes and Saunders's *Comparative Neuropathology* in 1962, and Fankhauser and Luginbühl's *Pathologic Anatomy of the Central and Peripheral Nervous Systems in Animals* in 1968.

A number of veterinary pathologists have made—or continue to make—extensive contributions to the literature of animal neuropathology. In addition to those individuals just mentioned, we would particularly like to acknowledge the work of Barlow, Dahme, Done, Harding, Markson, and Terlecki in Europe; Cordy, Hadlow, Koestner, Richards, and Young in North America; and Hartley and Jolly in Australia and New Zealand. Many younger individuals have stepped forward to continue the tradition of high standards established by these and other individuals.

EMBRYOLOGY AND ANATOMY: A SYNOPSIS

In early embryonic life, the central nervous system (CNS) develops in response to the formation of the notochord and the paraxial mesoderm. A midline zone of dorsal ectoderm thickens (the neural plate), invaginates to form

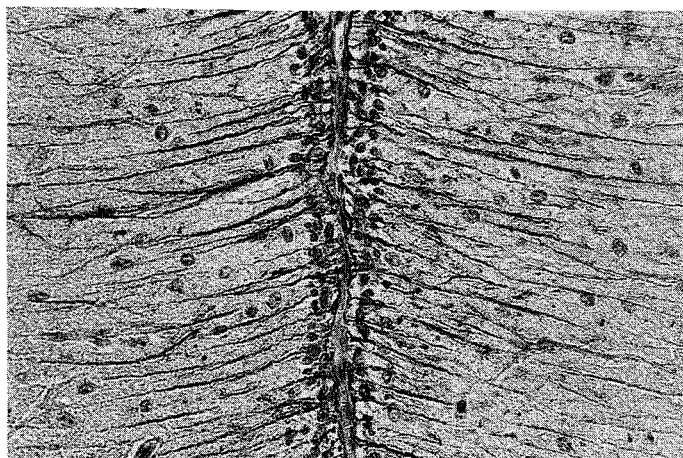


Fig. 1-1. Molecular layer of the cerebellar cortex, dog. Processes of astrocytes—derivatives of radial glia—are shown by GFAP immunocytochemistry. ($\times 350$.)

the neural groove, and then progressively closes, forming the **neural tube**. Closure generally proceeds rostrally and caudally. Subsequently, mitotic activity in germinal neuroepithelial cells lining the neural canal (the germinal matrix) gives rise to progenitor neurons and neuroglia. Cells so generated migrate away from the germinal zone to form the columns of gray matter in the spinal cord, various nuclei in the brain stem, and the nuclei and cortex of the cerebellum and cerebrum. The remaining cells form the ependyma of the central canal of the spinal cord and ventricular system of the brain. In the cerebrum, a subventricular zone of potential germinal cells persists postnatally adjacent to the lateral ventricles. Its role as a continual source of neuroglia and neurons is not well established. In the formation of the laminated neocortex, hippocampus, and cerebellar cortex, neuronal migration is guided by the processes of **radial glial cells** (Fig. 1-1),^{3,4} which in the developing cerebral hemispheres extend from the ventricular zone to the pial surface like the spokes on a bicycle wheel. Orderly neuronal migration involves the production and recognition of cell adhesion molecules, such as neural cell adhesion molecule (NCAM) and myelin associated glycoprotein (MAG), and substrate adhesion factors such as cytotactin, laminin, and fibronectin.^{5,6} Cells that fail to migrate to their predetermined region die in situ or may survive as heterotopic cell nests. Several patterns of disordered neuronal migration are recognized in humans.⁷ Radial glial cells form astrocytes in the differentiated nervous system,^{8,9} including the subpial glia limitans. Hirano and Goldman¹⁰ present evidence that both astrocytes and oligodendrocytes may have a common lineage from radial glial cells in immature spinal cord. In contrast, macroglial cells in the brain are derived from both germinal zone cells¹¹ and radial glia.

Differential growth rates in the head region gives rise to

three primary brain vesicles, the **prosencephalon** (forebrain), **mesencephalon** (midbrain), and **rhombencephalon** (hindbrain). Subdivision within the prosencephalon gives rise to the **telencephalon** with its paired cerebral hemispheres and to the centrally situated **diencephalon**. The differentiated neocortex of the cerebrum is folded into convolutions called **gyri**, with fissures termed **sulci**. The phylogenetically older portions of the cerebral cortex are the olfactory cortex and the hippocampus. Optic vesicles—the formative retinæ of the eyeballs—develop from each side of the prosencephalon, whereas the diencephalon contributes the neural lobe of the pituitary gland. The diencephalon consists of the epithalamus, thalamus, and hypothalamus. The rhombencephalon divides into the **metencephalon** (cerebellum and pons) and the **myelencephalon** (medulla).¹² Novel neuroanatomical features of the CNS in domestic animals have been reviewed by Koestner.¹³

A normal component of development in the nervous system is a genetically programmed neuronal cell death by a process of **apoptosis**. Normal development produces an overabundance of neurons. The mechanisms that trigger this apoptotic process are variable and just beginning to be understood.¹⁴ Genetic abnormalities may lead to excessive cell death in specific populations of neurons prenatally or postnatally (e.g., cerebellar Purkinje neurons). This premature neuronal death is referred to as **abiotrophy**.

Development of the CNS occurs over much of the period of intrauterine life (and continues postnatally) and so has the opportunity to be exposed to a number of teratogenic influences, including drugs, hyperthermia, nutritional deficiencies, infectious agents (mainly viruses), radiation, and heavy metals.^{6,15} Generation of neuronal populations occurs at distinct and finite times during development. There is poor compensation if progenitor cells are destroyed,¹⁶ which results in segmental hypoplasia (and sometimes concurrent dysplasia). Normal development of the neuraxis requires inductive influences operating between neural crest, mesoderm, and the neuroectodermal neural tube. In the vertebral column, anomalies of vertebral body development and of spinal cord formation may be seen together. The multitude of developmental disorders of the CNS are discussed in Chapter 2.

CELLULAR COMPOSITION OF THE CENTRAL NERVOUS SYSTEM

The CNS is constituted by parenchymal cells, which are the **neurons**, and by the **neuroglia**. Literally, neuroglia means “neural glue,” but our knowledge of the many functions of these cells has clearly advanced beyond that of simply holding the tissue together. The neuroglia are separated into macroglia and microglia: the macroglia are **astrocytes** and **oligodendrocytes**; the third glial cell type remains named as a **microglial cell**. Glial cells, although outnumbering neurons, were traditionally relegated to a secondary order of importance. That perspective has now

changed somewhat, and greater weight is given to the roles of neuroglia in normal functioning of the CNS.

Neurons are patently a diverse population. They range in size from the very small interneurons in the substantia gelatinosa of the dorsal horn of the spinal cord to the large ventral horn α -motor neurons whose axons project the length of the limbs. Neurons can be classified by their shape (e.g., unipolar, bipolar, multipolar), function (sensory, motor), the neurotransmitters utilized (cholinergic, peptidergic), facilitatory role (excitatory, inhibitory), and position in a fiber tract or pathway (upper motor neuron, interneuron—which accounts for the majority—and lower motor neuron). Some neurons within the CNS are part of the autonomic nervous system.

Astrocyte means starlike cell and is most applicable to the fibrous variety with their small soma and long, slender processes. An immature astrocyte could be termed an astroblast, but the term is infrequently used except in describing a group of rare tumors (astroblastomas). Oligodendrocytes have a small cell body and a few branched processes. Again the term oligodendroblast for an immature form seems to have found little favor. Microglial cells have a small cell body and a few ramified processes in the resting state. All of these constituents of the CNS—and others—are discussed in greater detail later in this section.

The brain and spinal cord are invested by the meninges (**dura**, **arachnoid**, and **pia**), which provide protection, a compartment for cerebrospinal fluid (CSF) circulation (the subarachnoid space), support for blood vessels, and a sheath for the cranial and spinal nerves. Within the brain and spinal cord are the ventricular system and central canal, which are lined by **ependymal cells** and the **choroid plexuses**, which produce the CSF. Circulation of the CSF moves from lateral, third, and fourth ventricles into the central canal or through lateral apertures at the cerebellomedullary angle into the subarachnoid space of the brain. CSF in the subarachnoid space drains via specialized **arachnoid granulations** into intracranial venous sinuses, with some draining into venous plexuses associated with cranial and spinal nerves. CSF may also cross the ventricular surface into the adjacent parenchyma.

THE LANGUAGE OF NEUROPATHOLOGY

Many of the terms applicable to pathological changes in extraneural organs find no place in neuropathology. Fatty change or cloudy swelling can describe reactions in the liver, kidney, or heart, but the CNS has unique populations of cells and neuropathology requires its own language. In some cases, the name of the normal structure (satellite cell, glial cell) is modified to describe a pathological reaction (satellitosis, gliosis). Most of these expressions are not applicable to other tissues.

A term commonly used to describe injured neurons is **chromatolysis**. It indicates breakdown (lysis) of the cytoplasmic Nissl bodies, which are cytosolic aggregates of

granular endoplasmic reticulum and free polyribosomes. In all but the very smallest neurons, there are Nissl aggregates visible by light microscopy, and these are the cells that may show this reaction. Chromatolysed neurons are swollen and rounded, and the nucleus typically takes an eccentric position. Classically, chromatolysis has been equated with the **axonal reaction** in which axonal interruption triggers the neuron to change its metabolic state and gear up to regenerate the axon. However, there are other causes of chromatolysis. **Satellitosis** is the proliferation of satellite cells secondary to neuronal degeneration. When this process occurs within the CNS, some view these reactive cells as largely oligodendroglial; others hold that any of the three neuroglia can participate. Satellitosis seems often to portend the imminent progression to **neuronophagia**, a process whereby the degenerate fragments of a necrotic neuron are removed piecemeal by macrophages. When the term **status spongiosis** is applied to neural tissue, there is a spongy vacuolation evident by light microscopic examination. This may occur from vacuoles within processes of the neuropil, vesiculation of myelin sheaths, or swelling of astrocyte or oligodendrocyte cytoplasm. The structural basis for status spongiosis often requires electron microscopic (EM) examination for its unequivocal resolution.

Gliosis is a common and nonspecific response of neuroglial cells in the CNS to many forms of injury: It is important in CNS inflammation but ischemic, traumatic, toxic, and other insults all seem capable of activating the neuroglia, in particular, astroglia¹⁷ and microglia. An area of the CNS that is gliotic is hypercellular because of glial cell hypertrophy, cell proliferation, or both phenomena. Increased cell numbers may result from proliferation in situ or recruitment, as glial cells can migrate. Transplantation studies have shown that immature astrocytes have a considerable capacity to migrate within the CNS.^{18,19} Studies of glial cell responses to a range of stimuli suggest that gliosis resulting from cell proliferation is more characteristic of microglia than of astroglia.^{20,21} **Microgliosis** is microglial cell proliferation, in which state the cells take on an elongated, slender profile. By tradition, a few specific arrangements of these reactive cells have been named, including microglial stars (focal clusters) and glial shrubberies (where they aggregate on cerebellar Purkinje cell dendrites). Gliosis that results in the generation of macrophages is commonly supplemented from the circulation, as can be shown by the diminished response following bone marrow irradiation.²² Astrocytic reactivity is **astrocytosis** or **astrogliosis**. These terms are often used interchangeably, although astrocytosis implies cell proliferation whereas astrogliosis conveys an increase in the numbers of filament-rich fibrous processes. Reactive astrocytes may stain for both glial fibrillary acidic protein (GFAP) and vimentin,^{23,24} as well as microtubule-associated protein 2 (MAP-2).²⁵ Interestingly, it seems that astroglia and microglia can elaborate reciprocal growth factors (i.e., astroglia produce microglial cell mitogens and vice versa),^{26,27}

and these are probably complemented from other CNS and non-CNS sources.^{28,29}

Of the three glial cell types, **oligodendroglia** are traditionally thought to be the least reactive to most forms of CNS injury; at one time, their ability to proliferate was in question. Normal oligodendrocyte turnover in the adult CNS is slow—1 to 2 years in rats—and may involve a pool of precursor cells as well as mature oligodendroglia.³⁰ However, satellite oligodendrocytes react to neuronal degeneration (satellitosis), and white matter cells proliferate early in demyelinating diseases.³¹ The ability of mature oligodendrocytes to divide following lysolecithin-induced demyelination has been shown.³² In response to surgical injury to the neocortex in adult mice, evidence of cell proliferation of mature oligodendrocytes (as well as astrocytes, endothelial cells, pericytes, and microglia) was found.³³ Maximal mitotic activity was found at approximately 72 hours.

Other terms will be encountered in the peripheral nervous system (PNS) in which there are **Renaut bodies**, **Büngner's bands**, **onion bulbs**, and more.

NEURONS

The CNS is a complex of systems that permit multiple concurrent activities at conscious and unconscious levels. We take as self-evident that the function of the nervous system depends fundamentally upon a diverse population of specialized cells known collectively as **neurons**. The neuron doctrine, brought to wide notice by the neurohistological studies of Ramon y Cajal,³⁴ is only a century in age. Ramon y Cajal adapted and modified the impregnation technique of Golgi, and these two scientists kindled the flame of investigations in neuroanatomy and neuropathology that continue to this day.

The neuron has a dendritic zone, a perinuclear perikaryon (the term soma equals the perikaryon plus the nucleus), and an axon. This holds true for all neurons in the CNS with the modifier that the proximal and distal processes differ considerably in their length and branching. The dimensions of neuronal perikarya vary considerably from one population to another, and their shapes range from approximately circular (granule cell neurons of the hippocampus or cerebellar cortex) to pyramidal (neocortex) to polyhedral (as in many brain stem nuclei). In paraffin sections, the nucleus and nucleolus are evident, as is a variable complement of cytoplasm (Fig. 1-2). Basophilic Nissl bodies are found in the cytoplasm in all but the smallest neurons; there is a clear, Nissl-free area at the axon hillock. Primary dendritic stems and proximal axonal segments can often be visualized. Ultrastructurally, the neuron has a large, centrally placed, ovoid nucleus with a prominent nucleolus. The cytoplasm is rich in stacked cisterns of rough endoplasmic reticulum (rER) and polyribosomes (together they equal Nissl granules), Golgi, and mitochondria; it has scattered intermediate filaments (neurofilaments) and microtubules, a few lysosomes and a few multivesicular bodies. Phosphorylation of

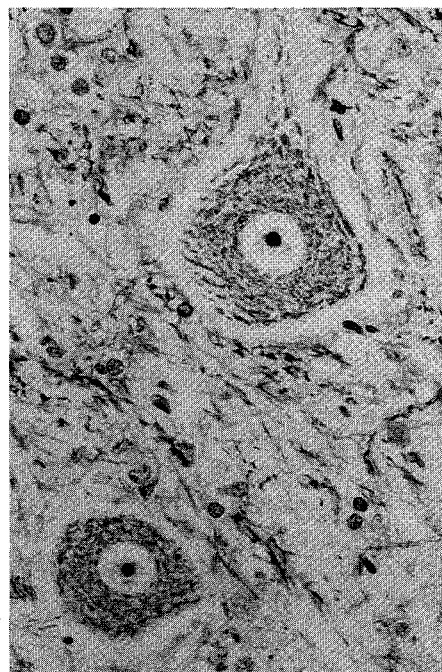


Fig. 1-2. Spinal cord, goat. Normal somatic motor neurons. (Luxol fast blue, cresyl echt violet, $\times 450$.)

the neurofilaments is essential for their assembly and transport along the axon,³⁵ and so diseases characterized by neurofibrillary pathology may be a consequence of deranged phosphorylation. Axons are seen to best advantage where tracts are sectioned longitudinally. They appear as faintly basophilic, elongated fusiform structures, often distorted (focally swollen) by the effects of fixation and processing. They are identified in a much more satisfactory way by silver impregnation techniques; the use of antisera or monoclonal antibodies to the axonal cytoskeleton has added a further level of sophistication to their study. Degenerating axons can be shown to advantage by the Nauta-Gygax technique and are common up to 24 months after injury, further attesting to the slow rate of repair of CNS degenerations.³⁶ The dendrites and axons contain neurofilaments, microtubules, mitochondria, and smooth endoplasmic reticulum (sER). Dendrites differ from axons in having Nissl bodies but only a sparse complement of filaments; only axons are myelinated. Axons terminate at boutons that form synaptic specializations on dendrites or somata with asymmetric membrane thickenings and aggregated synaptic vesicles.

Functionally, neurons are specialized for generating membrane action potentials that are conducted as an electrical impulse for the length of the axon. At the synapse, this electrical signal is converted into a chemical message that crosses the synaptic cleft to stimulate the next neuron in train. A single neuron is a link in a chain, and its loss has consequences for the chain (a fiber tract) as a whole. Secondary degeneration of neurons may follow: In the anterograde direction, this is referred to as **transsynaptic neu-**

ronal degeneration, and in the opposite direction it is **retrograde neuronal degeneration**. These patterns of neuronal loss are seen in humans and infrequently in animals, often related to the cerebellar cortex and its brain stem connections.

Viability and normal functioning of neurons demand a rich capillary vasculature to supply oxygen and glucose and remove wastes, an astrocytic syncytium to recycle neurotransmitters and extracellular K, and oligodendrocytes to maintain myelin internodes, allowing for energy-efficient saltatory conduction. It becomes self-evident that neurons can be directly or indirectly injured in many ways. Neurons have a high requirement for energy and are susceptible to impairment by various types of energy deprivation, such as ischemia. With virtually no exceptions, neurons lost from the mammalian CNS leave a lifelong deficit. Stem cells present in adult mammalian brain can be induced to differentiate into neurons (and astrocytes) in culture.³⁷ Presumably there is a problem with activating these progenitors in situ.

For neurons with long axons, the perikaryon represents only a tiny fraction of the magnitude of the cell. For example, a lower motor neuron may have a cell body that can be measured in micrometers (10^{-6} m) and an axon that projects for a meter or more. The sensory neurons of the spinal ganglia and the neurons of the spinocerebellar tract are also in this class. Consider the length of their axons in the giraffe: The dimensions of these single cells are quite remarkable.

Because axons lack ribosomes, they have no capacity for protein synthesis. As a consequence, the axon and nerve terminal depend on the perikaryon for their supply of all structural elements. Axonal transport systems are distinguished on the basis of direction (anterograde, retrograde) and rate of movement (see also PNS for details).³⁸ The bulk of the axoplasmic contents (cytoskeletal structures and cytoplasmic contents) is conveyed from the perikaryon by slow axonal transport, whereas fast transport delivers small vesicles and organelles. Recycling of effete organelles by lysosomal or ubiquitin pathways demands that such substrates be transported from the axon back to the soma, that is, in the retrograde direction. This unique arrangement of axonal physiology carries with it some inherent risks, particularly for those cells with long axons. It also raises the likelihood that some forms of neuronal injury (ostensibly affecting the cell body) will first be evident as dysfunction at the distal reaches of the axon. This is the important **dying-back hypothesis** of Cavanagh,^{39,40} which he envisioned as degeneration of an axon beginning at its furthest reaches and, in the face of continuing injury, progressing (dying back) toward the cell body. This concept has been modified slightly in the light of experimental investigations. It is now viewed as degeneration of the distal (but not necessarily the terminal) part of the axon, which then spreads both in the anterograde direction and back up to the neuronal cell body.

Dying-back neuropathies involve the longest central or peripheral axons, particularly those of large diameter. In summary, the neuronal cell body must (1) synthesize the needs of the axon (plasma membrane, cytoskeleton, synaptic vesicles), (2) deliver these to the axon, and (3) recycle waste products. Potentially, any process that interferes with these processes could result in distal axonal degeneration. Many are recognized in humans, particularly chronic intoxications.

Pathological reactions involve each component of the neuron (dendrite, perikaryon, and axon). It is important to bear in mind that all three elements are part of a single cell and that although this division is convenient it is artificial. Chromatolysis, Wallerian degeneration, and ischemic cell change are more fully discussed with the PNS or hypoxia, respectively.

Dendritic stems pass into the neuropil largely unrecognized in paraffin-embedded, H&E stained tissues, and so little is written of their reactions to injury. Most is known from Golgi preparations and from EM; for example, they are prone to accumulate inclusions that occur in other parts of the neuron, such as in the lysosomal storage diseases or in neuronal glycoproteinosis. Diabetes mellitus induces axonal dystrophy in the autonomic nervous system, and dendritic processes are affected concurrently.⁴¹ Dendrites of some neurons are richly endowed with receptors for L-glutamate and so are believed to be affected early in disorders mediated by excitotoxic neurotransmitters. Sporadically, dendritic changes in specific neuronal populations have been recognized in humans.⁴²

The **perikaryon** of the neuron houses the synthetic machinery of the cell from which vesicular and cytoskeletal elements are directed into the axon. Most neurons, which have Nissl flakes evident by light microscopy (LM), may undergo a form of degeneration known as **chromatolysis** (Fig. 1-3). This is revealed by cell swelling and by dispersion or loss of some or all of the Nissl bodies. Chromatolysis may be central, peripheral, or total, depending on the severity of the injury and the stage at which the affected neuron is examined. The interpretation of peripheral chromatolysis is somewhat unclear; some view it as a regenerative stage with restitution of perinuclear Nissl bodies. Chromatolytic neurons are found in a number of neurological disorders such as equine motor neuron disease; in canine, feline, or equine dysautonomia; and in swayback in lambs (copper deficiency). Some neurotropic viral infections produce chromatolysis, as do the inherited disorders that result in excessive neurofilament accumulation within neurons. Chromatolysis may also reflect the response of the cell body to the loss of its axon from traumatic, ischemic, or other causes, especially if the axon is interrupted close to the perikaryon. In such circumstances, the chromatolytic change is termed the **axonal reaction**, and it reflects a metabolic change in the neuron from its steady state toward its needs for axonal regeneration. Such include up-regulating mRNA synthesis for the production of structural cyto-

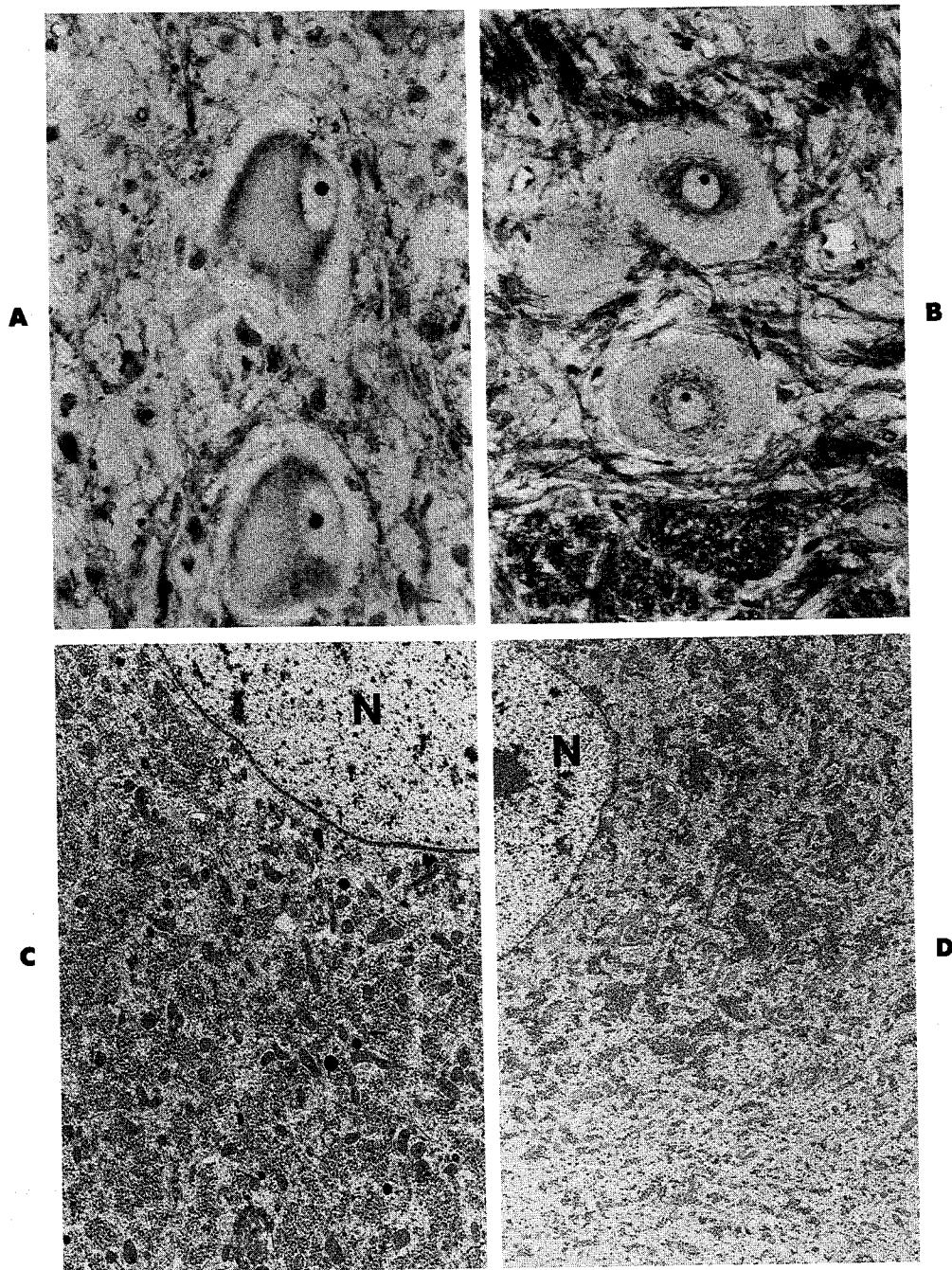


Fig. 1-3. A, Central chromatolysis, spinal cord, dog. (Luxol fast blue, cresyl echt violet, $\times 560$.) B, Peripheral chromatolysis, spinal cord, dog. (LFBCEV, $\times 350$.) C, Electron micrograph of a normal motor neuron, horse. N, Nucleus. Cytoplasm contains many Nissl bodies, mitochondria and a few dense bodies. ($\times 5850$.) D, EM demonstrating peripheral chromatolysis in motor neuron, dog. N, Nucleus. ($\times 3900$.)

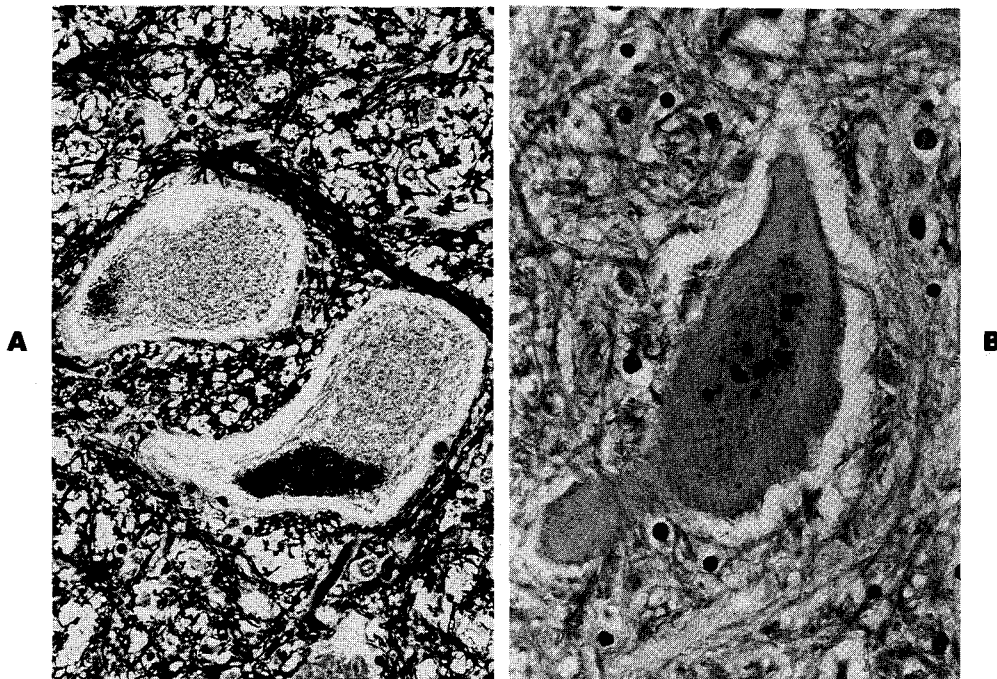


Fig. 1-4. Neuronal inclusions. **A**, Lipofuscin, seen as fine granules, which stain with Luxol fast blue. ($\times 350$.) **B**, Cytoplasmic inclusions in a shrunken neuron in equine motor neuron disease. (H&E, $\times 560$.)

skeletal elements (tubulin, actin) and axolemmal and growth cone membrane constituents³⁸ and down-regulating those proteins related to synaptic transmission. Despite these shifts in neuronal activity, axonal repair within the CNS is feeble. For motor neurons whose axons project to the PNS, survival is likely, whereas if the entire neuron lies within the CNS, chromatolytic degeneration is likely to proceed to neuronal atrophy.⁴³

Chromatolytic neurons in the CNS invoke a local glial cell response, particularly if their axons lie peripherally. Microglial cells proliferate, insinuate themselves between the degenerate cell body and its surface synaptic junctions, and strip the synapses from the perikaryal surface, deafferenting the cell.⁴⁴ Astrocytes up-regulate GFAP fibril production, but astrocytic proliferation is sparse.

A number of **cytoplasmic inclusions** (Fig. 1-4) are observed in neurons. They include the golden yellow **aging pigment** (often equated with lipofuscin) that accumulates in some neuronal populations with advancing age. In animals, **neuromelanin** is normally most evident in hypothalamic neurons but by EM can be found more widely distributed. Inherited or acquired **lysosomal storage diseases** result in cell swelling and a granular to vacuolar appearance of the cytoplasm due to a proliferation of cytosomes. **Lafora bodies** are PAS-positive polyglucosan deposits that may be encountered incidentally or in Lafora body disease. Brownish cytoplasmic inclusions in the thalamus and spinal cord are associated with **phalaris staggers** in ruminants. Eosin-

ophilic cytoplasmic inclusion bodies are found in degenerating neurons in equine motor neuron disease.⁴⁵ In humans, a number of neuronal cytoplasmic inclusions are recognized, including **Bunina bodies** (amyotrophic lateral sclerosis), **Hirano bodies** (Pick's disease, ALS, Parkinsonism dementia complex), **Lewy bodies** (Parkinsonism with or without dementia), and **Pick bodies** (Pick's disease).⁴⁶ Many **viral infections** result in the formation of amphophilic to eosinophilic intracytoplasmic and/or intranuclear bodies, consisting of varying proportions of viral proteins and cell organelles. **Cytoplasmic vacuoles** in neurons are an important hallmark of the spongiform encephalopathies such as scrapie and bovine spongiform encephalopathy. Some neuronal populations, such as the red nucleus in cattle, normally have scattered cells with large cytoplasmic vacuoles. Fine neuronal vacuolation may be evident in ischemic neurons, resulting from swelling of mitochondria or endoplasmic reticulum. **Neuronal encrustation** or **siderosis** describes neurons that have undergone necrosis and become encrusted with calcium and iron salts. In **Alzheimer's disease**, important histopathological features are the cytoplasmic neurofibrillary tangles and granulovacuolar degeneration of neurons. In a number of neurodegenerative human diseases, **ubiquitinated inclusions** can be demonstrated immunocytochemically within affected neurons.^{47,48} Ubiquitin is produced in response to cell injury; it binds to proteins that are to be degraded and guides them toward (mainly nonlysosomal) catabolism.

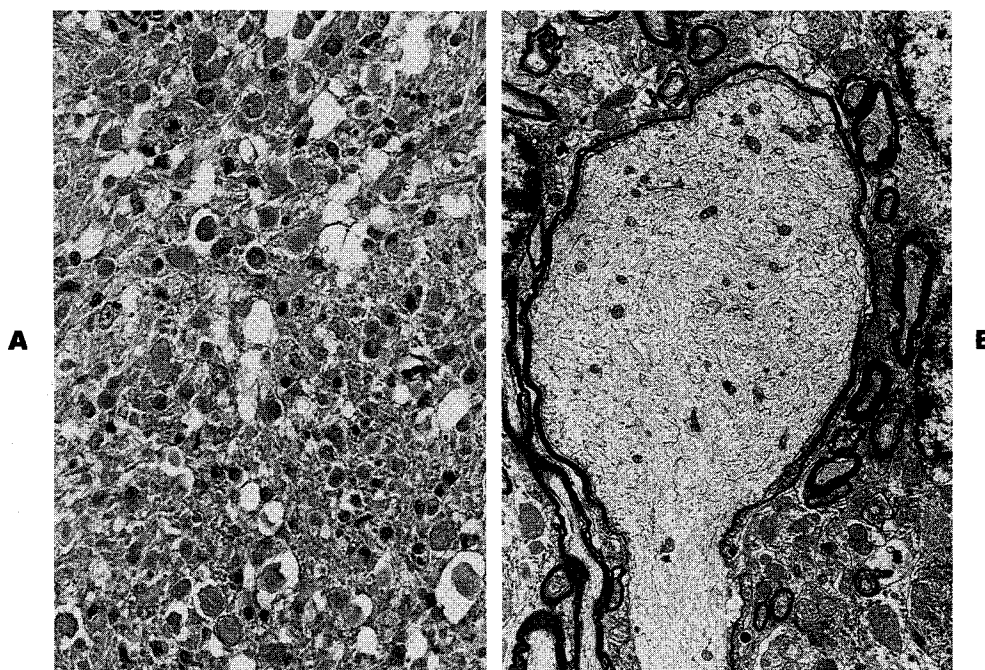


Fig. 1-5. Spheroids. **A**, Light microscopic appearance of spheroids (swollen axons). Edema disease, pig. (H&E, $\times 350$.) **B**, Electron micrograph of a spheroid; the axon is distended with neurofilaments. ($\times 5850$.)

The **axon** is dependent on the cell body for essential materials. As they are delivered by active transport mechanisms,⁴⁹ some axonal diseases are thought to result from a primary disorder of transport.^{50,51} Neuropathies that are characterized by swelling of the proximal axon segment with neurofilaments may be due to a disorder of slow anterograde transport. Characteristically, such diseases manifest a secondary alteration, namely atrophy of the distal portion of the axon (**somatofugal atrophy**) due to the failure of delivery of neurofilaments. Neurofilaments are the major determinant of axonal caliber; an insufficient supply leads to axonal atrophy. The neuron is susceptible to many insults (infection, intoxications, nutritional deficiencies), and so impaired transport probably underlies many forms of axonopathic change. Many **distal axonopathies** affect long axons because of the failure of a compromised cell body to maintain its axon.^{39,40} As the disorder progresses, degeneration spreads proximally along the axon. Some distal axonopathies may result from a failure of retrograde transport of axoplasmic debris accumulating at the terminus.⁵⁰ In a number of primary axonal diseases, pathological involvement occurs in both central (CNS) and peripheral (PNS) fiber projections. In these syndromes, degeneration of distal or subterminal regions of the axon is a common theme. One example is the distal axonopathy of vitamin E deficiency, which affects axons within the dorsal columns of the spinal cord and in the peripheral nerves. In delayed organophosphate poisoning, distal axons in both compartments degenerate. These two diseases are discussed with the CNS de-

generative disorders, as is also the axonopathy of Ibizan hound dogs. We have chosen to present other mixed, central-peripheral axonopathies in the chapter discussing PNS disorders. Specifically, these are the giant axonal neuropathy of German Shepherd dogs and progressive axonopathy of Boxer dogs. In both of these inherited disorders, considerable PNS involvement occurs such that electrophysiological and teased nerve studies are contributory to diagnosis. A central-peripheral distal axonopathy is reported in the Birman cat⁵² and is also discussed with the PNS.

Because of the constant anterograde and retrograde transit of axoplasmic organelles, axons react to many forms of injury by swelling.^{53,54} Focal axonal distensions are termed **spheroids** (Fig. 1-5). If caught in transection, they are approximately circular, smooth to granular eosinophilic bodies. They may stain uniformly or unevenly, sometimes giving a targetoid appearance. A longitudinal view reveals a fusiform shape, and spheroids of Purkinje cell axons are termed torpedoes. Those arising within myelinated axons remain ensheathed by an attenuated myelin coat or may be devoid of myelin. They vary from modest to huge axonal swellings.

Spheroids arise in a variety of circumstances,⁵⁵ and with each syndrome their distribution in the neuraxis (focal or diffuse, gray or white matter) and ultrastructural composition will vary. Ultrastructurally they are a mixture of neurofilaments, tubulovesicular structures, mitochondria, lysosomes, and membranous bodies. They are the pathological hallmark of **neuroaxonal dystrophies** and are regularly

found widely through the neuraxis in some lysosomal storage diseases, vitamin E deficiency states, and equine degenerative myeloencephalopathy. Spheroids are seen focally about areas of injury produced by wandering parasites, at the margins of infarcts, at sites of spinal cord compression, and as an incidental finding with aging. In the neuroaxonal dystrophies, the swellings involve distal or preterminal parts of the axon and so are commonly found in gray matter in proximity to neuronal cell bodies.

A process intimately associated with the axon is **Wallerian degeneration**. Waller was a student of peripheral nerve injury, and the changes in the distal segment that follow nerve transection are known as Wallerian degeneration. Degenerative changes, usually of lesser degree, affect the proximal sector also. A similar sequence of events follows axonal interruption in the brain and spinal cord, although there are a number of important differences. Some prefer to designate this process within the CNS as Wallerian-type degeneration, to emphasize that in several ways it differs from its counterpart in the PNS. Wallerian degeneration—fragmentation and dissolution of the distal part of the axon and digestion and removal of the collapsed myelin tube—proceeds more slowly in the CNS⁵⁶ than in the PNS. This may reflect differences in the signaling mechanism between the two systems or inaccessibility of macrophages to injured CNS compared to peripheral nerves.⁵⁷ It is a common observation that the removal of tissue debris from the CNS moves very slowly, often over months to years. An important point of variance between Wallerian degeneration in the CNS and the PNS is in axonal reconstitution. In the PNS, sprouts grow prodigiously from the point of axonal interruption, and several slender processes, which terminate in a bulbous growth cone, are guided by the preexisting basal lamina into a newly formed column of Schwann cells (Büngner's band). In the CNS, there is no basal lamina scaffold, and although oligodendrocytes can survive to some extent following the loss of their axon,⁵⁸ they do not form columns of cells to be innervated. Furthermore, oligodendrocyte myelin proteins are inhibitory to axon sprouting, which is feeble at best in brain or spinal cord. If the axons of CNS neurons are sectioned and then surgically transposed into a PNS environment, vigorous elongation of the fiber is seen. Thus the CNS population is not constitutionally unable to reconstitute a transected axon but is inhibited from doing so within the CNS.

In Wallerian degeneration, dissolution of the distal part of the axon is an active process rather than a passive event following the loss of substrates from the perikaryon.⁵⁹ Granular degeneration of the cytoskeleton results from the action of proteases, which are probably intrinsic to the axon. Subsequently, the myelin sheath fragments into chains of myelin ovoids that are slowly cleared by the action of phagocytic cells (Fig. 1-6). The degenerative process is thought to release macrophage trophic factors, for these cells are attracted to degenerate but not intact fibers. If, prior to nerve

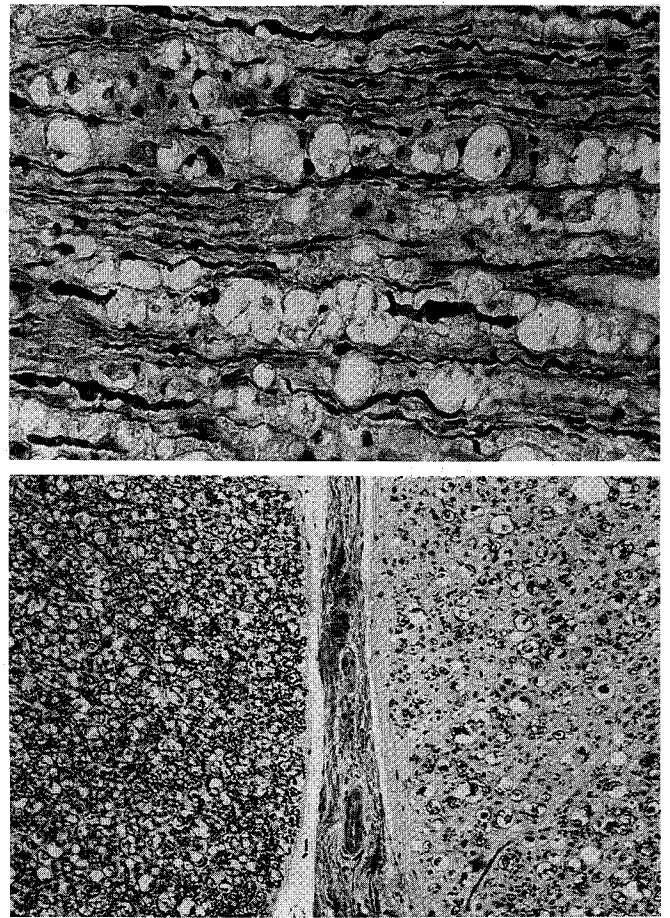


Fig. 1-6. Wallerian degeneration in the CNS. **A**, Spinal cord, pig. Notice disrupted axons and chains of digestion chambers. Neurofilament immunocytochemistry. ($\times 350$.) **B**, Spinal cord, goat. The funiculus with chronic degeneration is depleted of myelinated axons, which are replaced by reactive astrocytes. (Luxol fast blue, cresyl echt violet, $\times 140$.)

injury, animals are treated to diminish macrophage numbers, or if Wallerian degeneration is studied *in vitro* to deplete macrophage numbers or their access to the nerve, degeneration of the distal stump is delayed.⁶⁰ In the Ola mutant mouse, Wallerian degeneration in both the CNS and PNS proceeds more slowly than in control animals.⁶¹ This may be an intrinsic property of the axon⁶² or possibly a failure of either macrophage signaling or up-regulation of vascular adhesion factors.

Recruitment of hematogenous mononuclear macrophages to PNS fibers undergoing Wallerian degeneration is complement-dependent.⁶³ In particular, the C3 fragment seems to be important as a trophic factor for encouraging macrophage invasion of the degenerate nerve and in opsonizing myelin lamellae for phagocytosis via macrophage C3 receptors. The same may hold for the CNS, as complement antagonists (cobra venom) diminish demyelination in experimental autoimmune encephalomyelitis (EAE). Degen-

eration of myelinated axons in the CNS induces the expression of class II major histocompatibility complex (MHC) antigens on microglia, but degeneration of unmyelinated axons does not.⁶⁴

ASTROCYTES AND OLIGODENDROCYTES

It may seem unusual that we have chosen to discuss the reactions to injury of astrocytes and oligodendrocytes together. In the mature mammalian CNS, these are structurally and functionally distinct cell populations with quite disparate duties to perform. In the immature nervous system, however, intermediate or transitional forms with the features of both astrocytes and oligodendrocytes have been described,⁶⁵ and other investigations (CNS injury, CNS cells in culture) have revealed glial cells with dual phenotypes. Such include the expression of GFAP in immature oligodendroglia^{66,67} and galactocerebroside in reactive astrocytes.⁶⁸ Other workers question the existence of an intermediate cell type and suggest that these are really astrocytes.^{69,70}

The pioneering work of Raff and his collaborators indicates that the development of astrocyte and oligodendrocyte lineages in the fetal/neonatal CNS system is linked. Interrelationships between astrocytes and oligodendrocytes/myelin probably exist in developed tissue also; for example, type 2 astrocytes may be specialized for an association with myelin sheaths.⁷¹ Perinodal astrocytic processes are associated with the node of Ranvier,⁷² where they express a glycoprotein involved in cell-to-cell interaction.^{73,74} Furthermore, within the spectrum of glial tumors, mixed oligoastrocytomas are seen.

From studying glial cell development in culture by using a neuron-free substrate (rat optic nerve), Raff suggests that **astrocytes** can be classified as **type 1** (derived from one specific precursor) and **type 2** (derived from a distinct second precursor). The progenitor of type 2 astrocytes is designated the O-2A cell as in vitro it can give rise to oligodendrocytes or type 2 astrocytes, depending upon the culture medium in the dish.^{75,76} High concentrations of fetal calf serum drive differentiation toward astrocytes, whereas minimal levels result in oligodendrocyte development, which may be the default pathway. Tissue culture studies have shown that type 1 astrocytes secrete factors that influence proliferation and differentiation of the O-2A progenitor; platelet-derived growth factor (PDGF) and ciliary neurotrophic factor have come under scrutiny as two such mitogens and growth factors.⁷⁷ In chemotaxis assays, O-2A progenitors migrate toward PDGF, whereas type I astrocytes respond most strongly to C5a and laminin.⁷⁸ Basic fibroblast growth factor, PDGF, and insulin-like growth factor 1 seem to be important in oligodendrocyte development.^{79,80}

Several groups have confirmed Raff's identification of the O-2A cell dual lineage under tissue culture conditions,^{81,82} and the progenitor has additionally been demonstrated in adult rat optic nerve, a possible omnipresent stem

cell.⁸³ However, Raff's scheme may not hold for gliogenesis in all areas of the CNS. Neonatal rat spinal cord contains astrocyte precursors that differ from the type 1 or O-2A cells found in the optic nerve.⁸⁴ Further, cell lines with a bipotential capacity have been established which develop into cells with either astrocytic or neuronal characteristics.⁸⁵ Raff's proposals are not confirmed in all investigations,^{86,87} and the proposition has been made that these observations rather reflect glial cell plasticity as demonstrated under tissue culture conditions. Thus, to what extent the type 1 and type 2 astrocyte classification can be extended to the in vivo situation is arguable. Classically, histologists divided astrocytes into large **protoplasmic** forms in gray matter, which had few, short processes, and the **fibrous** form (mainly in white matter), which has many long, slender processes. Loosely speaking, type 1 astrocytes can be equated with protoplasmic forms and type 2 with fibrous astrocytes, but the demonstration of type 2 cells in tissue is problematic.⁸⁸

The intermediate filament⁸⁹ repertoire of astrocytes includes vimentin and glial fibrillary acidic protein (GFAP).⁹⁰ Immature astrocytes contain vimentin,⁹¹ and the switch in neuroglia from vimentin to GFAP production occurs at the time of myelination.⁹² In reactive or neoplastic astrocytes, coexpression of GFAP and vimentin can be shown. GFAP positivity is not limited to conventional astroglia. Radial glial cells, which provide a scaffold to guide the migration of newly differentiated neurons within the developing CNS, express GFAP. This is not altogether surprising, as some astroglia are derived from the radial glia. However, GFAP or closely related peptides are expressed by pituicytes of the neurohypophysis, retinal glial cells (Müller cells and retinal astrocytes), pineal sustentacular cells, nonmyelinating Schwann cells, and enteric glial cells.^{93,94} GFAP is also found in ependymal tanocytes. In human CNS tumors, GFAP expression has been found in oligodendrogliomas, understandably in oligoastrocytomas, ependymomas, and choroid plexus tumors, and it is found in a proportion of peripheral nerve sheath tumors thought to be of Schwann cell origin. More surprising, perhaps, is its consistent expression by myoepithelial cells in human pleomorphic salivary gland adenomas.⁹⁵

The many roles ascribed to astrocytes^{96-98a} point to the likelihood of heterogeneity and regional specialization of these cells.⁹⁹ Over the last two decades, our awareness of the number and diversity of **astrocytic functions** has expanded remarkably. In CNS development, the elongated processes of radial glial cells (astroglial precursors) guide the migration of neocortical, hippocampal, and cerebellar granule cell neurons. Astrocytes also form a sling to guide axons passing from one hemisphere to the other via the corpus callosum. Astrocytes have a structural (scaffolding) role in the developed tissue and respond to all forms of CNS injury by hypertrophy and increased synthesis of GFAP intermediate filaments.

It has been long appreciated that astrocytes have an im-

portant role in compartmentalizing the CNS. Astrocytes form a diffuse network of regularly spaced cells throughout the neuraxis,¹⁰⁰ joined cell to cell by punctate adhesions and gap junctions. This diffuse network delineates the outer and inner envelopes of the neuraxis (the **glia limitans**), which lies adjacent to the pia mater, the ependyma, and the margin of perivascular spaces. Astrocyte foot processes ensheath capillary vessels, where they induce formation of the endothelial blood-brain barrier. Astrocytes surround and isolate individual neurons and their synaptic connections and thus allow for selective transfer of neurotransmitters from one neuron to another. They are important in maintaining fluid and ionic homeostasis within the CNS and have a role in the uptake of excess neurotransmitter molecules. Local high concentrations of extracellular K may be handled by spatial buffering whereby K is transferred through the astrocytic syncytium to areas of low concentration.

The extent of astrocytic participation in immunological reactions in the CNS is unclear. Astrocytes can be induced to express MHC antigens, including class II antigens, during EAE or CNS viral infections.¹⁰¹⁻¹⁰³ Further, it has been shown that astrocytes may serve in vitro as antigen-presenting cells,¹⁰⁴⁻¹⁰⁶ thus functioning as accessory cells in immune reactions.¹⁰⁷ However, whereas astrocytes require exposure to γ -interferon to express MHC class II antigens, macrophage populations express them constitutively. Within the CNS, resident microglia are generally viewed as the representatives of the monocyte-macrophage system and hence have the primary responsibility in presenting foreign antigen to T lymphocytes. Perivascular microglia are strategically positioned for this role. Astrocytes are seen as second-order immune cells with a facultative capacity. In some diseases, they may have a crucial role to play; for example, they produce a number of cytokines and lymphokines important for antiviral activity.¹⁰⁸ Evidence has been provided that astroglial cells can initiate weak responses in CD8 cells but can activate secondary responses if T cells have first been primed by other antigen-presenting cells.¹⁰⁹ Hence, in vivo, macrophages may be quantitatively more important as antigen-presenting cells than astrocytes¹¹⁰ or cerebral endothelial cells,¹¹¹ which in culture have also been shown to present antigen to specific T cells. It has been proposed that astrocytes may be important for down-regulating immune reactions within the CNS.^{112,113}

Some astrocytes have neuronlike properties: They bind tetanus toxin, have receptors for a number of neurotransmitters, and have voltage-dependent Na⁺, K⁺, and Ca⁺⁺ channels.^{96,114,115} In part, electroencephalogram (EEG) tracings reflect astrocyte activities,⁹⁷ and they may be involved in long-range signal transmission within the brain.¹¹⁶ The possibility of signaling by neurotransmitters (such as glutamate and nitric oxide) from neurons to glia has been raised.⁹⁶

Newer developments include the possible role for some astrocytes at the node of Ranvier, immunological activities

Table 1-1. Some products of astrocytes

| Substance | Reference |
|---|-----------|
| Interleukins (1, 3, and 6) | 26, 118 |
| Interferons | 119 |
| Tumor necrosis factor | 120 |
| Prostaglandins | 118 |
| Cytotoxic factors | 121, 122 |
| Endothelin-3 | 123 |
| Angiotensinogen | 124 |
| Nerve growth factor | 125, 126 |
| Leukotrienes | 127 |
| Granulocyte and granulocyte-macrophage colony stimulating factors | 128 |
| Transforming growth factor- β | 129 |

(as previously noted), and their secretion of growth factors, mitogens, hormones, and other substances. Studies conducted principally in vitro have attributed the synthesis of a remarkable array of biological factors to astrocytes¹¹⁷ (Table 1-1).

Astrocytes respond to CNS injury by hypertrophy, increased GFAP expression and limited proliferation.¹³⁰ Increased mRNA for GFAP is detectable within 6 hours of experimental brain injury.¹³¹ Reactive astrocytes are evident by GFAP immunocytochemistry within 1 to 3 days and will remain prominent for approximately a month. Reactive astroglial cells are found considerable distances from the primary site of injury,¹³² probably as a result of astrocyte growth factors spread in vasogenic edema. Astrocyte mitogenic or growth factors¹³³ include myelin basic protein,¹³⁴ interleukin 1 and 6 and tumor necrosis factor,^{135,136} epidermal growth factor, fibroblast growth factor, and platelet-derived growth factor.¹³⁷ Astrocytosis is associated with the depletion of an inhibitor of epidermal growth factor receptors.^{29,138} Astrocyte-produced growth factors may act back on themselves in an autocrine fashion.

A proliferative ability of astrocytes is demonstrable in newborn animals,¹³⁹ seems to be more intense in adults,¹⁴⁰ and may be a property of a subpopulation (type 1 astrocytes).¹⁴¹ In the cerebral cortex, many astrocytes are normally GFAP negative in routine immunohistochemistry because GFAP filament concentrations are below the level of detection after tissue fixation and processing.¹⁷ Such cells become positive after cortical injury. However, less than 20% of these reactive astrocytes incorporate tritiated thymidine, indicating only modest cell division, which is largely limited to the first few days after injury.^{142,143} A study of reactive astrocytes for proliferating cell nuclear antigen found that only 5% to 6% were positive.¹⁴⁴

In routine H&E-stained sections of paraffin-embedded CNS tissue, normal astrocytes appear as naked ovoid nuclei with inapparent cytoplasm. The nucleus is poor in heterochromatin but may have a punctuate centrosome. In the gray matter, astrocyte nuclei are to be found in association with

the glia limitans, as satellites to some neurons or in the neuropil. They are approximately the size of the nucleus of a neuron in the neocortex and are larger than most identifiable oligodendrocytes or the more fusiform microglia. In white matter, astrocyte nuclei are often found within a chain of interfascicular oligodendroglia and may require GFAP staining to distinguish them. Electron microscopic features of astrocytes¹⁴⁵ are an ovoid, euchromatic nucleus and an electron lucent cytosol of polyribosomes, minimal rER, a few lysosomal granules, an occasional mitochondria, a variable presence of glycogen particles, and 10-nm filaments that are most conspicuous as bundles in the cell processes. In reactive cells a large nucleolus appears, the cytoplasm swells, intermediate filament density increases markedly, and microtubules may be seen. Astrocytes form gap junctions with each other and with oligodendrocytes. Where astrocytes are apposed to collagen fibrils, as at the glia limitans, they form hemidesmosomes and synthesize basal lamina. This is recapitulated in tissue culture.¹⁴⁶

The common astroglial response to CNS injury (Fig. 1-7) is manifest by the development of visible cytoplasm in the cell. Typically this takes the form of a broad, polygonal shape with the nucleus at the margin. Such large reactive astrocytes are deemed **gemistocytes**. The cytoplasm is smooth and eosinophilic and may have multiple small vacuoles at the margins. Sometimes binucleate or multinucleated astrocytes are formed. Some reactive astrocytes have a central nucleus and multiple long, slender processes, which often extend to the wall of blood vessels or the glia limitans. Such fibrous forms are best demonstrated by GFAP staining. Some less common reactive or degenerative changes in astrocytes are recognized. In hepatic and renal encephalopathy and some other disorders, astrocyte nuclei are seen in clusters of three or four and are swollen and clear. Such are described as **Alzheimer type II astrocytes** and are most conspicuous in gray matter. They show very poor production of GFAP in immunocytochemical preparations. In Wilson's disease of humans, **Alzheimer type I astrocytes** are seen; they have large, bizarre, lobulated or cleaved nuclei. They are exceptionally rare in animal neuropathology. **Rosenthal fibers** are ovoid to elongated, strongly eosinophilic, refractile bodies that occur within the cytoplasm of astrocytes. In humans, they are recognized in glial scars and in some astroglial tumors. They also occur widely in the CNS in Alexander's disease; the canine variants of this disorder are discussed with the leukodystrophies. By LM examination, GFAP immunoreactivity is found at the margins of Rosenthal fibers but can be demonstrated within the fibers by immunoelectron microscopy. Ultrastructurally, they consist of dense granular material with a high content of α - β -crystallin.¹⁴⁷

We have discussed the myriad and diverse physiological functions of astrocytes, which begin during development of the nervous system and continue throughout adult life. The

oligodendrocyte, in contrast, although having a crucial role to play, has a much more limited repertoire. It is possible that oligodendrocytes have important functions in the CNS so far unidentified; some of the activities now attributed to astroglia have been recognized relatively recently.

It is disconcerting to dissect the word oligodendrocyte and discover that it means nothing more than a cell with a few treelike branches. Nevertheless, this term has served the needs of the neuroscience community for about a century. Oligodendrocytes reside in gray matter and white matter. In the former, they are commonly found as **satellite cells** to neurons (Fig. 1-8). Their precise role is not understood but is assumed to serve some important metabolic function in neuronal homeostasis. Such satellite cells may also be reservoirs for remyelination after CNS white matter injury.¹⁴⁸ In white matter, oligodendrocytes are the most numerous of the neuroglia and are aligned in interfascicular chains (Fig. 1-9). Since the development of contemporary EM techniques in the early 1960s, it has been appreciated that **CNS myelin** is formed from the modified processes of oligodendrocytes. The myelin sheath is assembled about the axon in distinct segments known as **internodes**, which are separated from each other at the **node of Ranvier**. Myelin has high electrical resistance and low capacitance, allowing it to function as an electrical insulator.¹³⁴ As a consequence, conduction can only advance along the axon from one node to the next (saltatory conduction).¹⁴⁹ Were the depolarization continuous along the entire length of the axolemmal surface, the axon would have to be many times the diameter it is to allow for impulse conduction at rates characteristic of mammalian nerves (50 to 60 m/second). Conceptually, the immature oligodendrocyte is viewed as having a shape something like an octopus: a small cell body and a number of radiating processes. These processes insinuate themselves through the meshwork of naked axons in developing white matter tracts and become associated with individual axons by investing them. In some diseases, the oligodendrocyte may have problems sustaining its distally situated myelin sheath, somewhat akin to the metabolic stress placed upon neurons that have long axons.

It seems probable that oligodendrocytes are a heterogeneous population with some forming the sheaths of a few axons and others ensheathing many (up to 50). This introduces the concept that, given a minimal insult to the CNS, not all oligodendrocytes will be equally susceptible to the injury. Studies of oligodendrocyte-axon relationships in the developing feline CNS showed that in early myelinating areas (spinal cord), oligodendrocytes formed one or a few internodes about large axons.¹⁵⁰ In later developing tracts, oligodendrocytes produced several sheaths about smaller axons. The authors calculated that the larger myelin mass is produced and maintained by the former circumstance (one oligodendrocyte producing a single or very few internodes). The regulation of myelin sheath thickness for any given

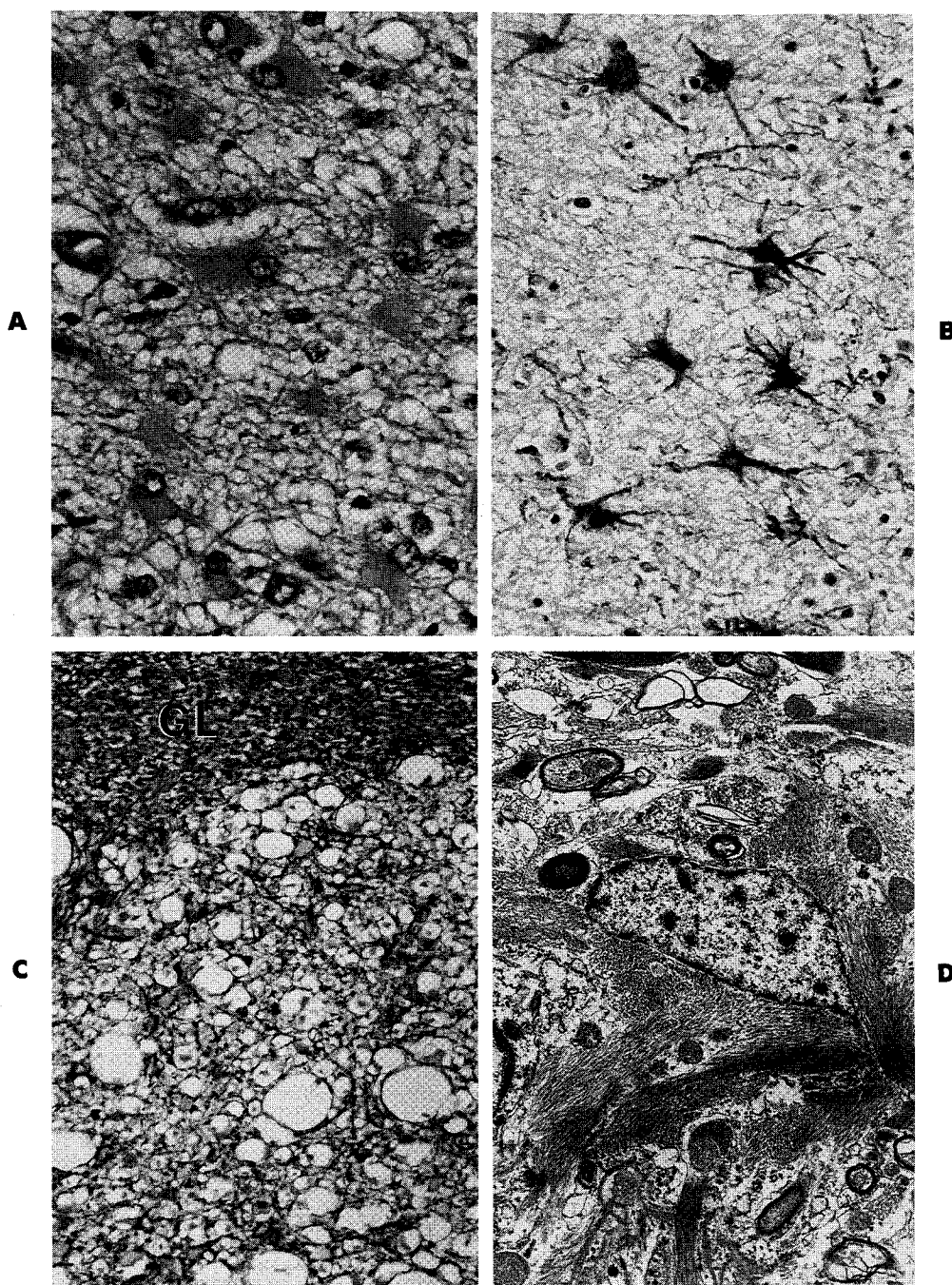


Fig. 1-7. Astrocytosis. **A**, Hypertrophic astrocytes (gemistocytes), cat. (H&E, $\times 560$.) **B**, Fibrillar astrocytes shown by GFAP immunocytochemistry, polar bear. ($\times 350$.) **C**, Astrocytosis in a congenital myelopathy, foal. Note the thickened glia limitans (*GL*) and astrocytic processes within the degenerate white matter. (GFAP, $\times 350$.) **D**, Electron micrograph of a reactive astrocyte, cat. Note pronounced cytoplasmic filaments. ($\times 8750$.)

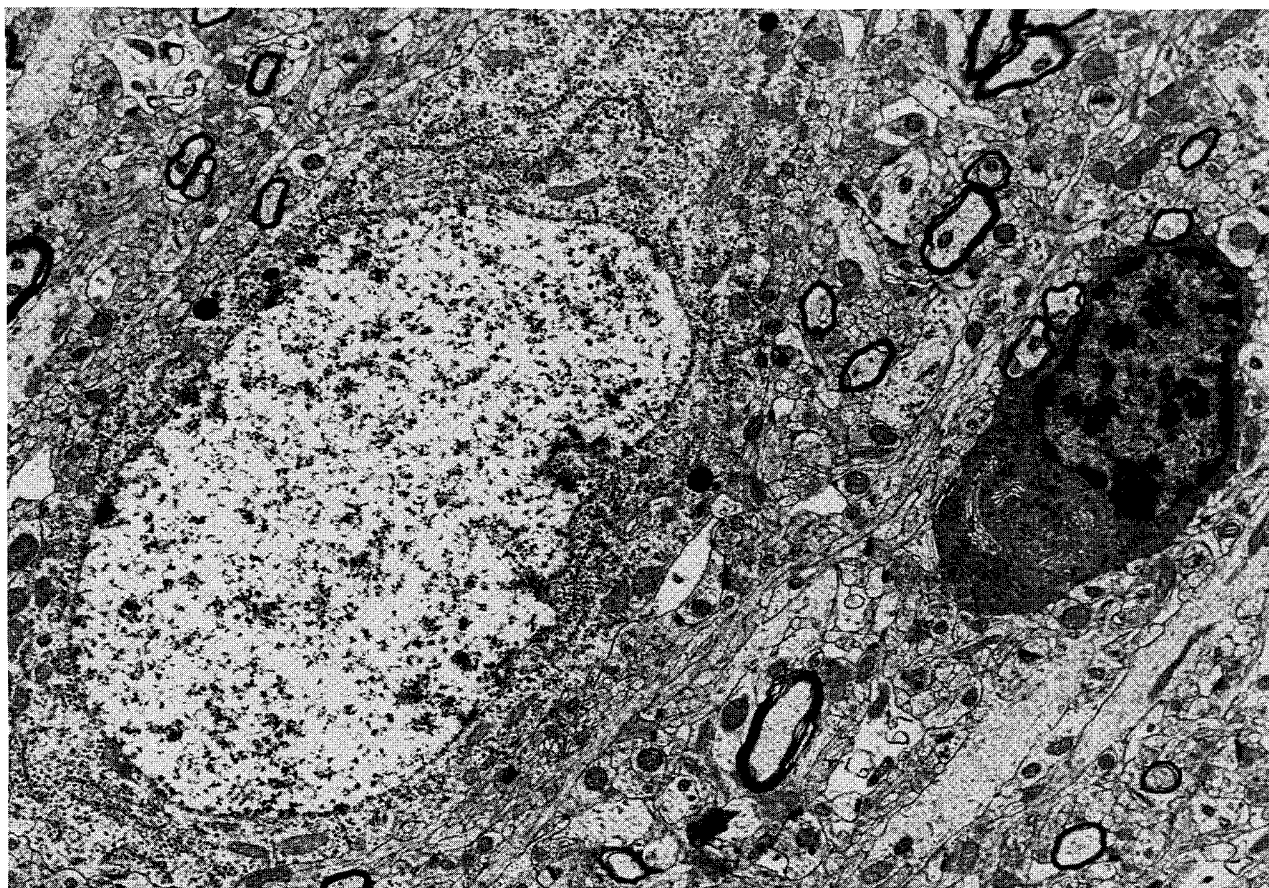


Fig. 1-8. Cerebral cortex, rat. Electron micrograph of a normal neuron and its satellite oligodendrocyte. ($\times 8090$.)

axon seems to be under local control.¹⁵¹ There is probably a relationship between the volume of a myelin internode and the area of the ensheathed axon.¹⁵²

Elimination of some axon ensheathments and remodeling of others seem to be intrinsic features of CNS development and mainly occur prior to compaction.¹⁵³ This may be effected by retraction of processes from axons or by degeneration of glial cells and even compacted myelin. Microglial cells with lipid inclusions are commonly found in white matter tracts during CNS development.

Myelination is an interactive event involving oligodendrocytes, axons, and astrocytes. Oligodendrocytes must be generated, and their processes need to respond to axonal signals by associating with and ensheathing the fiber. Oligodendrocyte mitogens such as platelet-derived growth factor, which can be produced by type 1 astrocytes, are thought to be important for this process.^{80,137} Blakemore and Crang's studies of remyelination (and by implication, myelination) show that the type 1 astrocyte is an important third party.¹⁵⁴ Axonal diameter seems to be one important criterion for myelin formation to begin, the minimal requirement being an axonal diameter of about 1 micron. The oligodendrocyte

must invest only that number of axons it can successfully myelinate, allowing for the fact that each axon will lengthen and expand in diameter with prenatal and postnatal growth. How this remarkable process is coordinated remains to be elucidated.

For myelin to form, an axon is encircled by multiple spirals of the fingerlike oligodendrocyte process. This does not happen at random, for axons myelinated by a single oligodendrocyte are usually wrapped in the same direction.¹⁵⁵ As the cell process compacts, its cytoplasmic contents are progressively extruded back toward the cell body. Eventually, the inner leaflets of the plasmalemma fuse with each other to form the **major dense line** while the outer leaflets of two apposed processes fuse to form the **intra-period** or **minor dense line**.¹⁵⁶ The periodicity (measurement from major to major or minor to minor density) is characteristic for CNS myelin and is about 15 nm; it is slightly longer in PNS myelin. At the EM level, a transected myelinated fiber shows the myelin sheath to have a repeating lamellar structure consisting of densities (which are proteins) and clear spaces (lipids). Myelin is approximately 70% to 80% lipid, of which the high cholesterol content

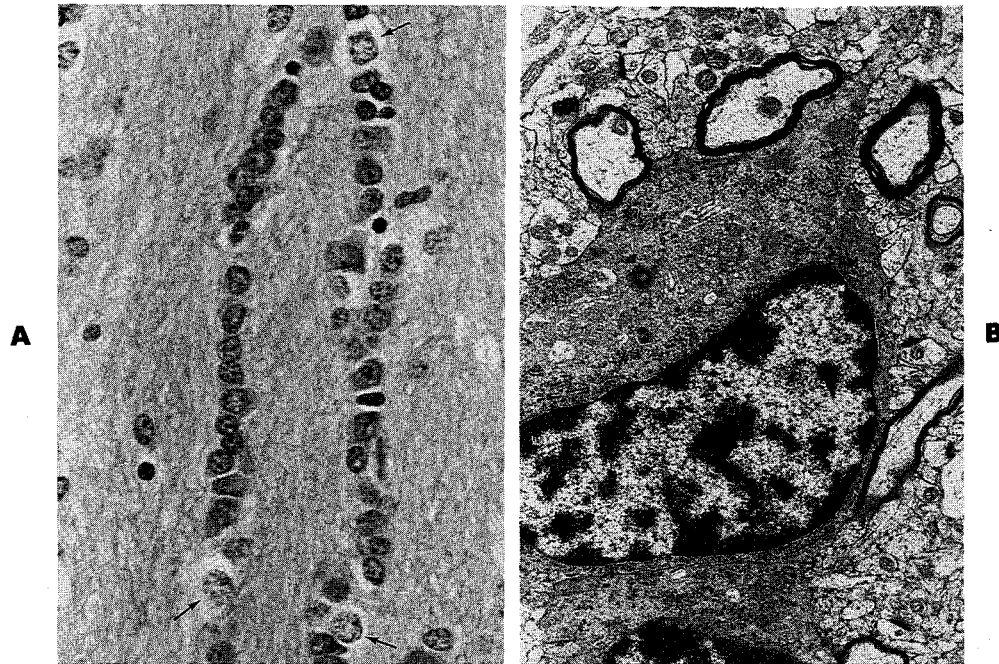


Fig. 1-9. **A**, Interfascicular glia, pig. These cells are predominantly oligodendrocytes with occasional astrocytes (*arrows*). ($\times 560$.) **B**, Electron micrograph of an oligodendrocyte and a few axons it has myelinated, rat. ($\times 12,500$.)

and particularly the cerebroside (galactolipids) are characteristic.¹⁵⁷ There are relatively few proteins in myelin membrane: The major proteins are the **proteolipid protein (PLP)** and **myelin basic protein (MBP)**; **myelin-associated glycoprotein (MAG)** is a minor component. PLP is concentrated at the intraperiod line, MBP at the major dense line, and MAG at the periaxonal space. PLP and MBP are thought to play structural roles in maintaining the myelin sheath and MAG to serve as an adhesion molecule between oligodendrocyte and axon. The synthesis, structure, and putative role of these myelin proteins in health and disease are reviewed by Campagnoni,¹⁵⁸ Lemke,¹⁵⁹ and Ikenaka and associates.¹⁶⁰ Oligodendrocytes and the myelin sheath also contain a number of intrinsic enzymes, such as carbonic anhydrase II and cyclic nucleotide phosphodiesterase. Myelin is a very stable structure with a long half-life (measured in many months) compared to other membranes.

The myelin internode terminates at either end in specialized paranodal **lateral loops** of uncompacted oligodendrocyte cytoplasm, which are joined to each other by desmosomes and to the underlying axon by zonulae occludentes. The node of Ranvier accommodates multiple astrocytic processes that converge toward the axolemma.⁷² It has been suggested that astrocytes may synthesize voltage-sensitive sodium channels for the axon,⁷⁴ which are concentrated at the node. When myelin formation is complete, the terminal innermost loop of the spiral (adjacent to the axon) is designated the **inner tongue** or loop; the **outer tongue** or loop connects to the soma of the oligodendrocyte.

Schmidt-Lantermann incisures, areas of uncompacted oligodendrocyte cytoplasm, are much less common than in Schwann cell myelin.

CNS myelin formation begins during life in utero and extends for a variable period in the postnatal phase. The degree of myelination at birth is a measure of maturity of the tissue; in humans, myelination continues during the first few years of life.¹⁶¹ The pattern of myelin development has been studied in humans and some animals. Often the impetus has been the necessity to determine what is normal in the face of a hypomyelinating disorder, such as Border disease in sheep. Myelination occurs in waves within regions of the CNS (often tracts), rather than as a continuum throughout the whole organ. In sheep, myelination is initiated in the spinal cord and parts of the brain stem by about 60 days of gestation; the hippocampus, diencephalon, and cerebellum by 80 days; the cerebrum by 100; and the rostral commissure and corpus callosum by 130 days of gestation.^{162,163} At the completion of the ovine gestational period (around 145 days), myelin is mature in most regions. Myelination proceeds in a caudal to rostral direction, usually beginning in the phylogenetically oldest tracts. Brain development is sensitive to many detrimental effects; general undernourishment (protein-calorie deficiency) results in diminished brain size and a reduced concentration of myelin.¹⁶⁴

Gross inspection of the transected brain from a fetus shows that immature (unmyelinated) white matter is grayish and the junction between gray and white matter areas less conspicuous than in mature tissue. In routine light micro-

scopic preparations, myelin in the fetal brain and the neonate (to about 4 weeks of age) is pale staining and may appear hypercellular. In mature tissue, myelin is eosinophilic and homogeneous to slightly fibrillar, the latter indicating its association with fascicles of axons. In transversely sectioned white matter tracts, the myelin sheath can be seen encircling a central axon, but this is not as well preserved in paraffin-embedded tissue as is PNS myelin. Furthermore, myelin is prone to vacuolar artifact if the tissue is autolyzed.

In H&E-stained paraffin sections, oligodendrocytes are traditionally recognized by virtue of their small, spherical, and moderately heterochromatic nucleus and inapparent cytoplasm. By EM,¹⁴⁵ three forms are identified: light, medium, and dark oligodendrocytes.¹⁶⁵ It has been suggested that this sequence is a developmental progression from least mature and myelin-forming (light) to most mature and myelin-maintaining (dark) oligodendrocytes. This interpretation has been questioned, as some investigators find light oligodendrocytes in mature CNS tissue. From light to dark cell types, there is decreasing cell size, increasing nuclear heterochromatin, and increasing electron density to the cytoplasm. In dark cells, the Golgi stacks are conspicuous and the matrix of the rER is pallid. Centrioles are common in canine oligodendrocytes. All types contain mitochondria, polyribosomes, and microtubules, but intermediate filaments are lacking. An occasional cytoplasmic Pi body may be observed. Ultrastructurally, it is usually impossible to observe continuity between an oligodendrocyte and the axons it is myelinating in mature tissue because of the distances between these two points. However, this relationship can be observed during development of the CNS.

Oligodendrocytes are involved in pathological reactions in gray and white matter. Satellite oligodendrocytes proliferate in response to degeneration of neuronal perikarya (**satellitosis**). However, removal of degenerate neurons by phagocytic action requires the influx of professional macrophages, either transformed microglia or blood monocytes. The pathological reactions of most concern involve the myelin sheath. It must be remembered that the oligodendrocyte and its myelin sheath are an anatomical unit, but there are important differences in chemical and immunological terms. **Demyelination** is the destruction of a normally formed myelin sheath, leaving the axon naked but otherwise unscathed. This process can also be termed primary demyelination to distinguish it from secondary demyelination, in which event myelin loss is a consequence of axonal degeneration. The axon can survive deprived of its myelin sheath, but the myelin sheath cannot exist if its central fiber disintegrates. As demyelination progresses, conduction of impulses becomes asynchronous, slows, and eventually stops.

In demyelinating diseases such as multiple sclerosis (MS) (Fig. 1-10) and many forms of experimental autoimmune encephalomyelitis (EAE), the axons are spared but may show long-term regressive changes.¹⁶⁶ However, in those few diseases of animals in which primary demyelination can

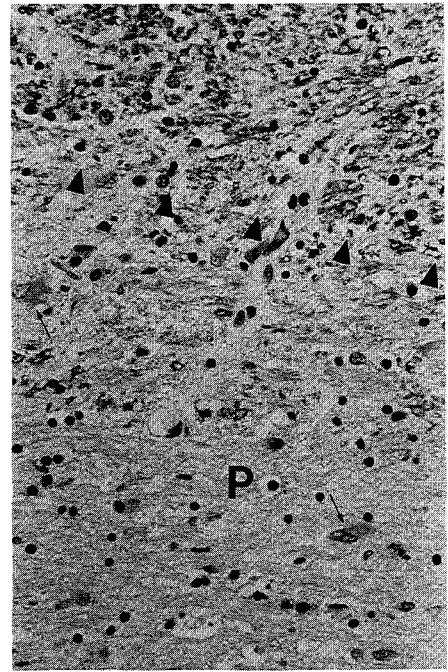


Fig. 1-10. Multiple sclerosis, human. Center of the plaque (*P*) is demyelinated and contains a few reactive astrocytes (*arrows*). Note the sharp demarcation (*arrowheads*) between the plaque and intact white matter. (Luxol fast blue, cresyl echt violet/GFAP, $\times 140$.)

be demonstrated—canine distemper, visna, caprine-arthritis-encephalitis syndrome—there is usually a component of concurrent axonal injury that varies in severity from case to case and within individual cases from one area to another.

A process that selectively destroys myelin internodes while leaving the underlying axon intact must be very specific in its actions. It is suggested that myelin damage could occur by bystander mechanisms (see the section on inflammation of the CNS in this chapter), but we find little appeal to this proposition. Inflammatory mediators are often spilled in the neuroparenchyma, but extensive demyelination is distinctly uncommon. Selective myelin loss would occur should the myelinating oligodendrocyte be destroyed, yet in multiple sclerosis, the most important of the demyelinating human diseases, the myelin sheath rather than the myelin-forming cell appears to be the target.¹⁶⁷ Viral infections that affect oligodendrocytes are known but in only a few is this thought to explain myelin loss.

Demyelination of modest degree probably accompanies many forms of white matter injury. In animals, myelin injury is characteristic of hepatic encephalopathy, the aminoacidopathy maple syrup urine disease, intoxication caused by the rodenticide bromethalin or hexachlorophene, and in globoid cell leukodystrophy in which condition a substrate accumulates which is toxic to oligodendrocytes. In all of these disorders there is probably some primary myelin loss demonstrable, but it is of secondary importance in the pathogenesis of the disorder as a whole. Chronic white matter

edema is associated with myelin loss and sclerosis in humans, but survival of comparably affected animals for the necessary duration to manifest such changes probably does not occur.

Myelin breakdown occurs in a limited number of ways. Myelin vacuolation is one, a nonspecific indicator of an oligodendrocyte insult, and is a change that in some circumstances is reversible.¹⁵² Ultrastructurally, intramyelinic edema is seen as splitting of the myelin sheath at the minor dense line. The large loops of myelin so formed produce the sponginess in white matter seen by LM. Such change may attract macrophages (as in canine distemper), and large fragments of myelin are directed into phagosomes and degraded to neutral lipids. Sometimes a fine vesicular change occurs within the myelin lamellae, or they are converted to reticular arrays.^{168,169} Often this transformation into honeycomb or tubular arrangements affects the outer myelin lamellae and may be the result of soluble inflammatory mediators such as tumor necrosis factor, lymphotoxin, complement, immunoglobulins, or proteases.¹⁶⁷ A different form of demyelination involves removal of compact myelin by the processes of macrophages that breach the myelin sheath and progressively strip away myelin lamellae.¹⁷⁰ This process has been recognized in spontaneous and experimental demyelinating diseases. Whereas removal of large myelin fragments seems to proceed by cell processes that encircle the segment, small myelin droplets may be taken up by clathrin-coated pits on the surface of macrophages.^{171,172} This may involve immunoglobulin acting as a ligand. Cells thought to function as phagocytes of myelin debris are resident microglia and blood-borne monocytes. It is recognized that astrocytes can participate also,^{172,173} and even phagocytosis by oligodendrocytes has been recorded.^{174,175}

Despite the major lipid composition of the myelin sheath, proteolysis is the main biochemical pathway in demyelination.¹⁷⁶ Proteinase activities have been studied in MS, EAE, and related disorders and are typically maximal in the area of demyelination, elevated in the borderline zone, and normal in more distant unaffected white matter. Macrophages produce a number of acidic and neutral proteases, and astrocytes are also a recognized source.¹⁷⁷⁻¹⁷⁹ By immunoblotting or immunocytochemistry, it is possible to document the sequential loss of individual myelin proteins.^{180,181} In those demyelinating diseases that follow primary injury to oligodendrocytes, the early loss of MAG in the developing white matter lesion is a useful clue.

Because of the importance of the human demyelinating disease multiple sclerosis, a number of model systems have been devised to explore the pathogenesis and therapeutic approaches to CNS demyelination. The most extensive studies are of **experimental autoimmune encephalomyelitis** (Fig. 1-11), which has been investigated in small laboratory animals (rats, guinea pigs, mice, and rabbits) and also larger animals, including primates. EAE can be induced actively by inoculation with complete myelin (or purified compo-

nents) and appropriate adjuvants, less successfully with isolated oligodendroglia,¹⁸² or passively transferred with sensitized T cells. By manipulating the genetic background of the host and the protocol for disease induction, it is possible to induce monophasic or remitting-relapsing disease. Affected animals show progressive deficits from tail paralysis to total paraplegia. Physiological studies of the effects of experimentally induced demyelination in EAE (or following injection with demyelinating antisera) have been reported.^{183,184} With demyelination, there is slowing in conduction velocity and finally conduction block.¹⁸⁵

EAE is a T cell-mediated disease. Direct injury to the oligodendrocyte-myelin unit by cytotoxic T cells is not thought to be important,¹⁸⁶ but a battery of humoral factors has been implicated.¹⁸⁷ These include T cell products,¹⁸⁸ tumor necrosis factor (a product of macrophages and astrocytes),¹⁸⁹ complement and perforin,^{190,191} and lymphotoxin.¹⁶⁷ Oligodendrocytes are sensitive to pore-forming factors and shed membrane attack complexes by vesicle formation,¹⁸⁶ as do other cells. Oligodendrocytes, rich in iron, are also sensitive to free radical injury. In EAE, an interplay between antibodies to myelin/oligodendroglial glycoprotein (MOG) and MBP-reactive T cells has been demonstrated: EAE induction in the presence of antibody to MOG and T cells amplifies the clinical deficits and the areas of demyelination.¹⁹²

There is an encyclopedic literature on EAE, and it has taught us much about many aspects of neurobiology (induction of CNS inflammation, remyelination after acute and chronic injury, important encephalitogenic molecules) beyond its immediate relevance to MS. Other animal models are the viral infections that produce CNS demyelination. Most studied are Theiler's disease and JHM coronavirus in mice and rats, but also canine distemper and some others.

In an attempt to elucidate the role in demyelination played by the multitude of potential factors such as viruses, antibody, T cells, and complement, *in vitro* models of demyelination were devised. That used most extensively is the organotypic culture system, maintained in Maximow chambers or roller tubes. Employing fetal (or neonatal) CNS tissue, the fragments grow and mature in culture with myelin formation. This paradigm has been extensively exploited by Bornstein and Raine and many other investigators.¹⁹³⁻²⁰² Other studies have employed aggregated cultures and cultures of isolated oligodendrocytes.^{188,203}

A question of major significance for human medicine is how efficiently can demyelinated zones within the CNS repair, that is, remyelinate.²⁰⁴ Studies with some chemically induced forms of demyelination would suggest that the normal consequences of CNS demyelination is remyelination,¹⁵² beginning within a few days of the injury. The failure of full restitution is more likely to be due to inhibitory mechanisms than to an intrinsic inability of the CNS to remyelinate.¹³⁴ There is a temporal factor, however: The capacity for remyelination is most evident after acute injuries

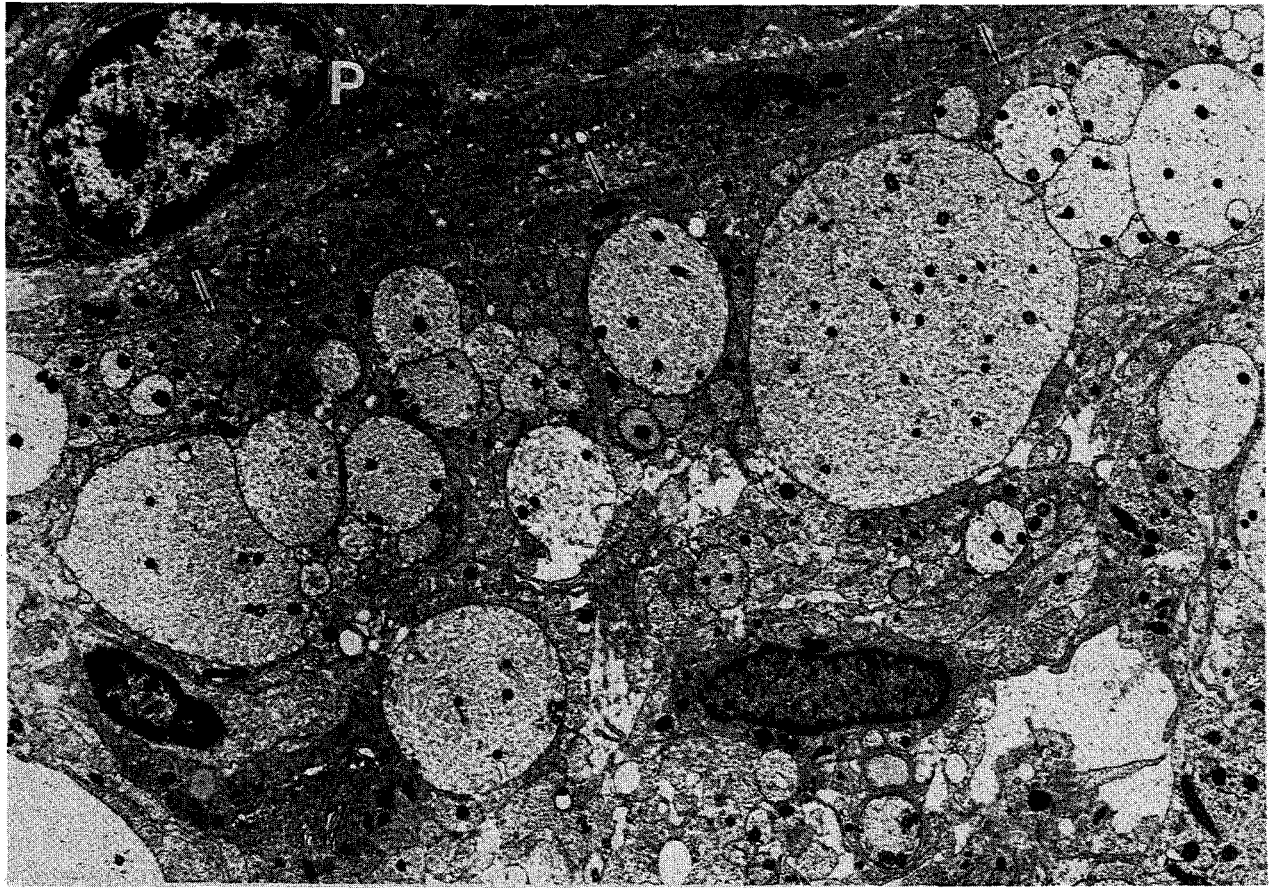


Fig. 1-11. Experimental autoimmune encephalomyelitis, rabbit. Demyelinated axons are seen within a background of astroglial processes. Arrows indicate the spinal cord glia limitans. A plasma cell (*P*) is part of a perivascular cuff. ($\times 5300$.)

and tends to decline with chronic, persistent disorders.

With remyelination, the internodes formed in repair are thinner and shorter than the original segment, as occurs also in the PNS. However, even a modest degree of remyelination may facilitate return of conduction. Remyelination of a small proportion of axons is well recognized in MS²⁰⁵ and related disorders²⁰⁶ and occurs with considerable efficiency in some experimental demyelinating disorders. For example, following cuprizone intoxication in mice, remyelination in the rostral cerebellar peduncle follows withdrawal of the compound from the diet.²⁰⁷ Remyelination has been observed during recovery from JHM coronavirus encephalitis in mice.²⁰⁸ Following Theiler's picornavirus infection in mice, remyelination is enhanced by treatment with antiserum to spinal cord homogenate. How this treatment acts is not known—perhaps by stimulating the growth or differentiation of glial progenitor cells.²⁰⁹ In this murine encephalomyelitis, there is a dramatic increase in oligodendrocyte proliferation in areas of demyelination.²¹⁰

The signals that instigate remyelination have been explored, for they may be open to manipulation in the patient.

Potentially, failure to repair may lie with axonal signaling or failure in the generation of new oligodendrocytes, their migration to, or association with the axon.¹⁵² The source of remyelinating oligodendrocytes in the adult CNS is controversial. There are two options: differentiation of a resting progenitor or replication of mature oligodendrocytes.^{30,21} The capacity for mature oligodendrocytes (attached to myelin) to proliferate has been suggested.²¹² The existence of progenitor cells in human brain tissue, which in culture will develop into oligodendrocytes, has been shown.²¹³

EPENDYMA AND CHOROID PLEXUS EPITHELIUM

Ependymal cells line the ventricles of the brain and the central canal of the spinal cord. Where invaginated by the tela choroidea, they project into the ventricular space as the choroid plexuses of the lateral, third, and fourth ventricles. These lining cells are locally modified into **choroid plexus epithelium**. Ependymal cells along the ventricular surface are usually flattened and elongated. Some ependymal cell and choroid plexus cells are a cuboidal to columnar epithe-

lumen with central to basally situated nuclei. Their apical surfaces are folded into microvilli, and they have long, slender cilia projecting from a basal body. The lateral cell margins, close to the apical surface, are joined by zonulae adherentes. Basally, the choroid plexus epithelium has a continuous basal lamina.

The fetal ependymal layer has several roles to play in CNS development and shows regional areas of differentiation within the developing brain.²¹⁴ Ependyma are involved in axonal guidance and in supporting radial glia, which are important for immature neuron migration. Ependymal differentiation is delayed until sufficient numbers of neurons are generated in the periventricular neuroepithelium. Cerebral hypoplasia or dysplasia may result from primary ependymal abnormalities.²¹⁵ Both in utero and postnatally, ependymal cells serve as a barrier between the neuroparenchyma and the CSF. However, they have more than mechanical functions as they have high oxidative enzyme activities and are a metabolically active population.²¹⁶ Part of the absorption of CSF is thought to occur across the ependymal layer into parenchymal blood vessels, and the ependyma probably have both absorptive and secretory functions. The ependymal layer contains a dual population, comprising the conventional ependymal cells and long, process-bearing ependyma known as **tanocytes**, which are most common in the wall of the third ventricle.²¹⁷ Their precise role remains uncertain. It has been proposed that tanocytes may be the source of some human CNS tumors such as astroblastomas.²¹⁸

With the exception of neoplasms, ependymal cells and choroid plexus cells are viewed as bystanders in most pathological events within the neuraxis in the sense that they are largely nonreactive cells. A few viral infections of the fetal nervous system result in ependymal cell infection, and receptors for viruses have been shown on ependymal cells.²¹⁹ Ependymitis may lead to hydrocephalus due to obstruction to CSF flow at the rostral aspect of the mesencephalic aqueduct where it is most narrow. Mumps and parainfluenza viruses are known causes of hydrocephalus. A number of inflammatory disease processes involve the ventricular surface (e.g., feline infectious peritonitis, equine infectious anemia), and ependymal cells are prone to be injured and lost. The extent of their proliferative capacity is uncertain and seems to be limited, as surface defects are commonly observed in these diseases. In suppurative leptomenigitis and ventriculitis in neonates, extension through the ventricular surface is common, whereas the pia seems to offer a more impenetrable barrier.

The microvillus surface of the choroid plexuses and the ependyma (in some regions) are populated with blood-derived monocytes, lymphocytes, and other leukocytes, which collectively have been given the name **Kolmer cells**.²²⁰⁻²²² They are probably comparable in function and activities to peritoneal macrophages. The choroid plexus may offer an important pathway to the brain in systemic diseases.²²³ Some

forms of bacterial leptomenigitis may begin at the choroid plexus, resulting from bacteria-infected monocytes migrating from the circulation to the ventricular surface to replenish Kolmer cells.²²⁴ Some viral infections, such as canine distemper encephalomyelitis (CDE), result in choroid plexus epithelial infection²²⁵ leading to the shed of virus into the ventricular system. Accordingly, it is common to find CDE lesions in white matter (such as in the cerebellar medulla) that is adjacent to CSF pathways. Some viruses that infect ependymal and choroid plexus epithelial cells bud from specific regions of the plasmalemma (either apically or basolaterally), which may be of importance for viral spread into the tissue.²²⁶ Within the CNS parenchyma, viruses are often transmitted along axons and bud at synaptic membranes for neuron-to-neuron passage.

The vascular bed of the choroid plexus is reminiscent of the renal glomerulus. Therefore, it is not surprising that the choroid plexus is affected in immune complex diseases with immunoglobulin and complement deposition.^{227,228} This is particularly prominent in systemic lupus erythematosus in humans and animals and in mesangiocapillary glomerulonephritis in sheep (see immune-mediated encephalomyelitis on p. 114). In many forms of encephalomyelitis, focal areas of inflammation within the stroma of the choroid plexuses are common. Hyalinization of the collagenous stroma of the choroid plexuses occurs with aging. In mature and aged horses, small, harmless cholesterinic granulomas are common in all choroid plexuses. Occasionally, the plexuses of the lateral ventricle may be replaced by large cholesterinic granulomas that act as space-occupying lesions. In CNS lymphomas, neoplastic cells may be found in the perivascular spaces, leptomeninges, and choroid plexus.

MICROGLIAL CELLS AND MACROPHAGES

Approximately 70 years ago, del Rio-Hortega applied a silver carbonate stain to developing CNS tissue and identified populations of positively stained cells. As his silver impregnation technique labelled macrophages, small cells (microglia), and subpial mesenchymal cells, he proposed a relationship between these elements. Del Rio-Hortega believed that the microglial cells were of mesodermal origin, derived from pial and microvascular mesenchyme, functioned as macrophages, and so constituted part of the reticuloendothelial system. Thus, unlike the other neuroglial cells, which are generated in the ectodermal periventricular germinal matrix of the developing neural tube, microglial cells were viewed as having a distinct extraneural lineage.

The origin of the microglial cell, the range of functions it performs within the CNS, and its relationship to macrophages derived from blood monocytes are areas of continuing controversy and uncertainty. The views expressed in the literature on the ontogeny of the microglial cell fall into two camps. A minority view is that these are neuroectodermal cells, derived from the same lineage that produces astrocytes and oligodendrocytes.²²⁹ In early ultrastructural

studies of these cells, Vaughn and Peters²³⁰ described microglia as a third neuroglial cell type and the term type-3 glia is sometimes still used. This putative relationship of microglial cells with the macroglia is based on studies of glial differentiation by EM and autoradiography.²³¹ Immunological studies showing shared antigenic epitopes in astroglia and microglia have been reported,²³² which may be significant or simply fortuitous. It is also curious that within human teratomas, areas of neuroectodermal differentiation with neurons and astroglia have also been accompanied by microglial cells.²³³ The interpretation remains open whether such cells are part of a neuroectodermal germ cell lineage or represent mesodermal cells that have invaded and colonized the neoplasm. De Groot and others²³⁴ proposed that most resting microglial cells are endogenous to the CNS and so are of neuroectodermal origin, whereas brain macrophages, evident in the neonatal period, are derived from the bone marrow.

The majority view holds that microglial cells are of mesodermal origin.²³⁵ Many investigators believe that the data support an origin from hemopoietic cells in bone marrow²³⁶⁻²³⁸ and specifically from monocyte-derived cells, which migrate to and reside within the CNS.²³⁹⁻²⁴² Proponents of the bone marrow—monocyte—microglial cell lineage extrapolate from events observed during CNS development and assume that throughout life, monocyte progenitors continue to trickle into the CNS in very low numbers²⁴³ to replenish spent microglia, which in their inert form are viewed as resting, potential macrophages. Thus, the microglial cell is seen as a member of the monocyte-macrophage system, specialized by virtue of the tissue in which it resides and functions, as are the osteoclasts of bone or the Kupffer cells of the liver. Microglia express some but not all of the antigenic determinants of bone marrow or circulating monocytes; proponents of the monocytic lineage hypothesis would argue that this reflects their tissue specialization. Resting tissue macrophages may normally subsist in a somewhat undifferentiated state until activated by tissue injury.²⁴¹

Some studies, while not specifically addressing the issue of microglial cell lineage, have attempted to refute the association between blood-derived cells (monocytes) and microglia.^{22,244} The issue of the derivation of the microglial cell has resurfaced with the development of sophisticated analyses now possible with contemporary biotechnological techniques. Proponents of both theories have provided data to support their contentions, with the result that data abound but the issue remains undecided. In this book, we have held to conventional wisdom while awaiting definitive proof otherwise.

Microglial cells are difficult to stain specifically in tissue, and this has greatly hindered their study. In routine H&E preparations, only the nucleus is evident, having a slender ovoid to fusiform shape and dense heterochromatin. In some profiles, the nucleus takes on a slender pyramidal shape,

being wider at one end and tapering at the other. In normal CNS tissue, microglia are evenly distributed in gray and white matter.²⁴⁵ In the gray matter, they are found as neuronal satellites (Fig. 1-12), around blood vessels, and free in the neuropil, and in the white matter within tracts of myelinated fibers. Microglia seem to constitute a minority of the three glial cell types, accounting for only 5.5% in one quantitative study.²⁴⁶ Microglial cells also occur in the neurohypophysis²⁴⁷ and the retina.²⁴⁸

The CNS is endowed with a number of macrophage-microglial populations.²⁴¹ They are conspicuously disposed at surfaces of the brain and spinal cord and about blood vessels, as well as within the neuroparenchyma. There are meningeal macrophages within the subarachnoid space, as well as similar cells on the surfaces of the choroid plexus and ependyma.^{220,249,250} A capacity for phagocytosis by leptomeningeal fibroblasts, independent of free mononuclear macrophages, has also been demonstrated.²⁵¹ A population of perivascular cells that adhere to the vessel wall enclosed by basal lamina are a source of macrophages. These have been described as pericytes²⁵² and pericytal microglia,²⁴⁶ but other studies suggest that these perivascular cells are probably bone marrow—derived macrophages and not pericytes or smooth muscle cells.^{253,254} A separate population, situated within the parenchyma between astrocytic foot processes and extending to the basal lamina, consists of the perivascular microglia. They are monocyte-derived cells²⁵⁵ and express or can be induced to express MHC class II antigens. Thus they are ideally situated to present antigen to hematogenous T cells and may be a component of the blood-brain barrier.²⁵⁶ Blood-derived phagocytes include neutrophils and the more highly capable monocytes. The largest population of endogenous brain macrophages is the microglial cells.²⁴¹

Traditionally, silver carbonate impregnation has been used to demonstrate the branching cytoplasmic processes of microglial cells. More recently, histochemical techniques such as nonspecific esterase²⁴¹ and nucleoside diphosphatase²⁵⁷ have been employed. Microglial cells bind some lectins including *Ricinus communis* agglutinin 1, mistletoe lectin, and *Griffonia*.^{235,258,259} They can also be identified by a battery of monoclonal antibodies raised to diverse macrophage populations: MAC-1 and MAC-3,²⁴¹ HAM-56,²⁶⁰ and OX42.^{239,245} They express complement (C3) and Fc receptors,^{245,261} the B lymphocyte marker LN-1,^{232,262} the leukocyte adhesion factor β -2 integrin,²⁶³ and the leukocyte common antigen CD45, which seems to be specific for cells of bone marrow origin.²⁶⁴

The electron microscopic features of microglial cells in domestic and laboratory animals have been reported.^{230,246,265} They have an ovoid nucleus with dense clumped heterochromatin and a single nucleolus. The cytoplasm is of a density intermediate between an astrocyte and a dark oligodendrocyte. The characteristic features are elongated strands of rER and variable numbers of primary and sec-

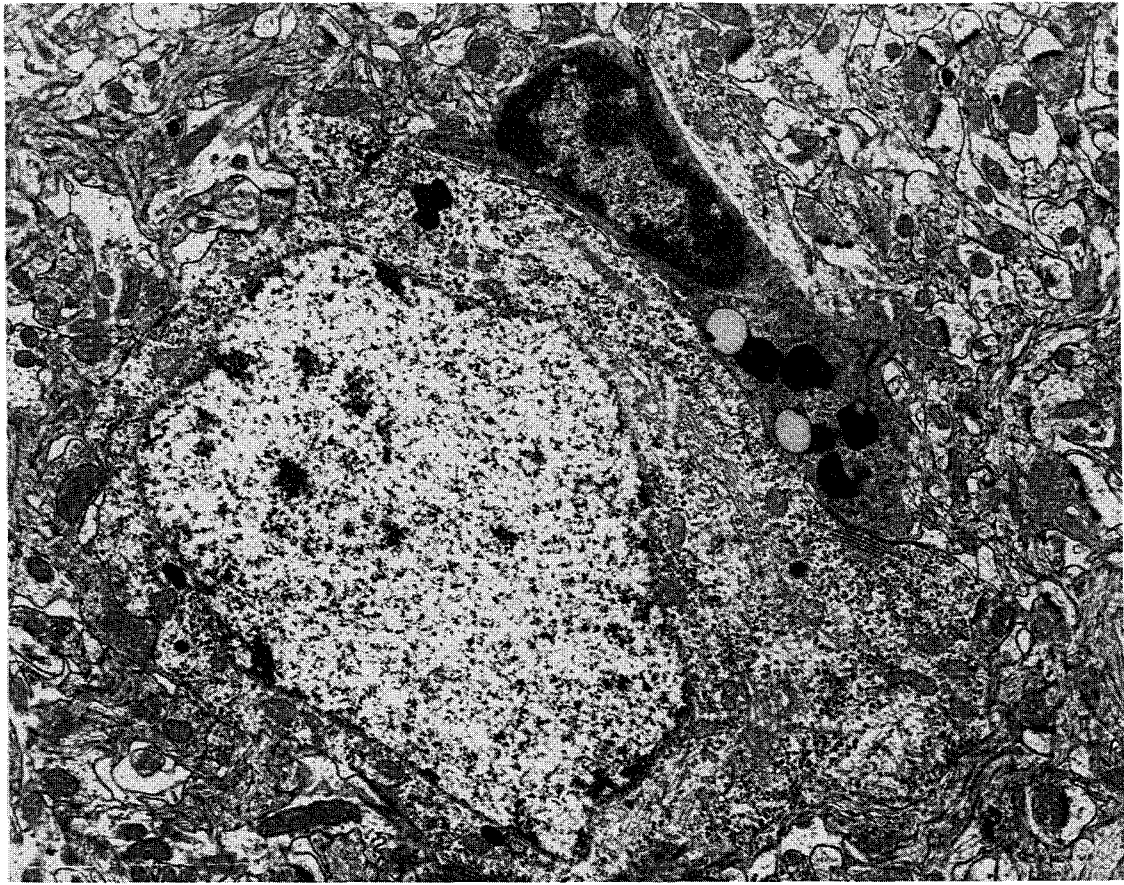


Fig. 1-12. Cerebral cortex, rat. Normal neuron and its satellite microglial cell, which has a few lipofuscin granules. ($\times 13,300$.)

ondary lysosomes and residual bodies. Sometimes residual bodies, lyre bodies, and other inclusions are present. A few microtubules may be observed in the cell processes. Golgi cisternae and mitochondria are inconspicuous.

At least three phenotypic forms of CNS microglial cells have been identified. Their relationship to each other is uncertain, with the result that they have several names, which adds nothing but confusion to the issue.

1. **Resting microglia** in mature CNS tissue are described as **ramified** or **dendritic** microglia. As shown by silver carbonate or more contemporary techniques, they have small, oval cell bodies and several slender, branching processes. In postnatal life, resting microglia are thought to transform into an ameboid form in response to severe CNS injury such as laceration, infection, or ischemia.
2. **Ameboid microglia** are conspicuous during the late fetal and neonatal period. They have swollen cytoplasm with fewer cell processes. Considerable degeneration occurs normally during CNS development, with loss of neuronal populations and remodeling of white matter tracts.²⁶⁶⁻²⁶⁸ Ameboid microglial cells are thought to function as scavenger cells during this pe-

riod of CNS maturation. They may also have secretory activities, producing angiogenic and glial growth factors.⁶¹ Ameboid mononuclear macrophages may also be derived from perivascular cells, meningeal cells, and infiltrating blood monocytes. This has tended to confound attempts to study microglial cell dynamics and to define the source of end-stage CNS macrophages, which are known variously as compound granular corpuscles, fat granule cells, or gutter cells (Fig. 1-13, A).

3. **Reactive or rod-shaped microglia** lack the processes of resting forms but may have cytoplasmic vacuoles and lysosomes. They are typically found in response to neurotropic infections (often viral) (Fig. 1-13, B) and some other forms of neuronal injury. Characteristically, their heterochromatic nuclei are long and slender, and as single cells they may be mistaken for vascular endothelia. Rod-shaped microglia incorporate bromodeoxyuridine, supporting the contention that this is the form of microglia that undergoes proliferation.²⁶⁹ These cells seem to participate in phagocytic activities, for they are seen about areas of neuronophagia in viral infections and degenerating neu-

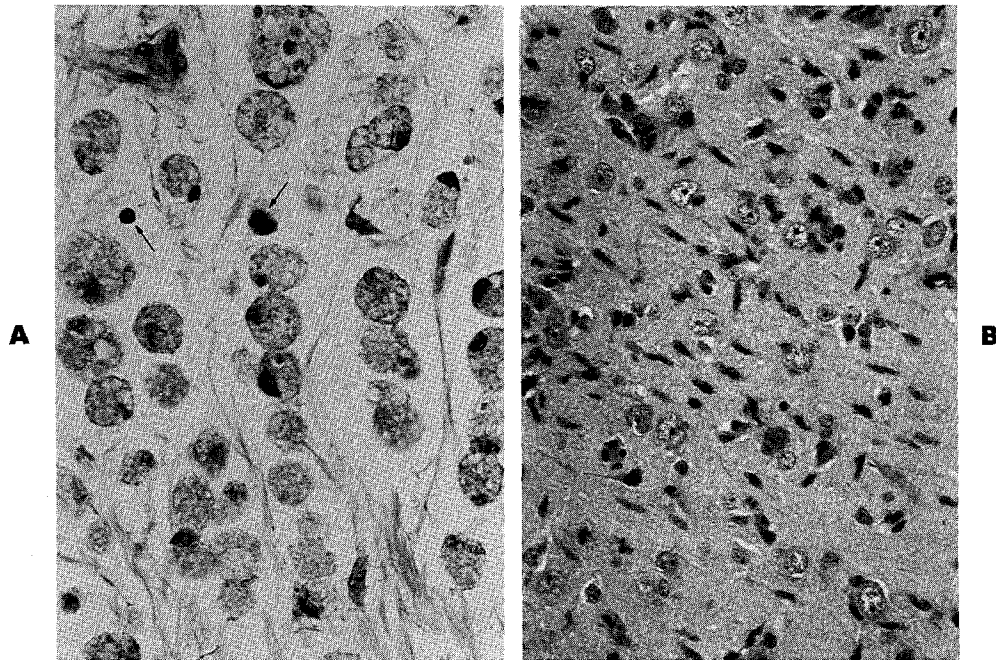


Fig. 1-13. **A**, Gitter cells, cerebral infarct, dog. Compare the size of these distended macrophages with lymphocytes and plasma cells (arrows). (Masson's trichrome, $\times 560$.) **B**, Microglial cell proliferation (rod cells), viral encephalitis, dog. (H&E, $\times 350$.)

ronal perikarya in motor neuron disease. Sites of prior neuronal death and phagocytosis may be marked by a cluster of microglial cells, some bearing lipofuscin pigment. Ameboid and reactive forms of microglia are highly phagocytic.²⁴¹

Microglial cells have an array of functions that are imperfectly documented. Rounded, ameboid brain macrophages seem to be important in removing the endogenous debris resulting from cell death and tract remodeling inherent in normal CNS development.²³⁹ Similar activities in mature nervous tissue are more widely recognized. A "graded response" to injury in the mature CNS has long been recognized.²⁴² Typically, subtle injury (such as that resulting from peripheral axotomy) triggers a reaction by the intrinsic microglia, while inflammatory or necrotizing insults also attract blood-borne phagocytes. The response also varies with age. Retrograde neuronal degeneration can be induced by removing part of the visual cortex and then examining the lateral geniculate nucleus. In the neonate, this procedure elicits a prompt response of mature macrophages to the degenerating thalamic nucleus. In contrast, in the adult, neuronal degeneration evolves more slowly, and the histiocytic response is slower and more protracted, mediated mainly by ramified microglia.²⁷⁰ These authors found no evidence for transitional forms between ramified and ameboid microglia and proposed that they may originate from the same bone marrow precursor but act under different conditions of cell death within the CNS.²⁷⁰

Investigators are beginning to study the chemotactic sig-

nals that activate intrinsic microglial cells and/or attract circulating monocytes to areas of injured brain tissue. If a peripheral nerve is sectioned to induce neuronal chromatolysis in its central (CNS) nucleus, microglial cells divide and strip (displace) synapses from the somata of affected neurons. If, however, the neurons are killed, such as by injection of ricin into the nerve or by explanting the nucleus into culture (the neurons die), the activated microglia develop into brain macrophages.^{271,272} These macrophages, of apparent endogenous (CNS) origin, newly express myelomonocytic cell antigens.²⁷³

Brain macrophages have a number of important duties, some unique and others shared with macrophages in other tissues.

1. They function as accessory cells in immune responses. Contemporary studies in mammalian immunology have established that antigen-specific T lymphocytes recognize their target only when there is concurrent expression of appropriate major histocompatibility complex (MHC) molecules.^{274,275} Cytotoxic (CD8+) T cells require MHC class I molecules, whereas helper T cells (CD4+) identify class II structures. Both classes of MHC molecules are expressed at low or undetectable levels in normal CNS tissue. Class I molecules are found on a wide variety of cells in the body. In contrast, cells bearing (or capable of being induced to express) class II molecules are limited to bone marrow monocytic cells and their derivatives in tissue (dendritic cells, reticulum

cells), monocytes, tissue macrophages, and B cells. Of the cells intrinsic to the CNS, microglia are the population that mainly expresses MHC class II antigens in inflammatory lesions.^{276,277} Accordingly, microglia are seen as forming an immune network within the CNS.²⁷⁸ The question arises as to what extent other neural elements can act as antigen-presenting cells. Studies with dissociated CNS cultures have shown that cerebral endothelial cells and astrocytes can be induced to express class II molecules after such treatments as γ -interferon. What remains uncertain is to what extent these observations *in vitro* can be related to the whole animal. Many investigators feel that indigenous microglia (or blood-derived macrophages) are the professional antigen-processing and -presenting cells^{20,279} and that astrocytes and perhaps endothelia have this function facultatively. Indeed, astrocytes may be important for down-regulation of immune responses within the CNS.²⁰ Constitutive expression of MHC class II has been recorded in the rat at about 25% of microglial cells²³⁶ and about 13% of microglia in normal human white matter²⁸⁰; it is subject to variations from technical factors.²⁸¹

2. Macrophages have a number of endocytic and phagocytic activities that may involve clearing infectious agents from the CNS. Large agents (protozoa, fungi) may be phagocytosed directly, but often this follows opsonization of the microbe and its uptake via Fc receptors. Successful pathogens sometimes use this pathway to gain access to macrophages in which cells they can replicate.²⁸² Macrophages are essential for the removal of tissue debris, whether arising from necrobiosis or a pathological process. Laden macrophages migrate slowly toward perivascular spaces to exit by way of the vasculature or in the CSF.²⁸³ Macrophages play a critical role in demyelinating diseases and Wallerian degeneration. They strip compact lamellae of myelin from axons in many demyelinating disorders of the CNS and PNS.¹⁷⁰ Myelin droplets may be taken up into macrophages by clathrin-coated pits.^{171,172} In Wallerian degeneration, macrophage infiltration is essential for degeneration and disposal of the injured axon segment. In macrophage-depleted animals, degeneration of the distal segment is greatly prolonged.
3. Macrophages produce an array of mediators of tissue injury, including proteases, interleukins, tumor necrosis factor, prostaglandins, reactive oxygen species, complement factors, and also growth factors.^{242,284} Secretory activities of CNS macrophages are thought to augment the inflammatory response. However, in HIV infection it has been hypothesized that CNS tissue injury may be caused by monokines secreted by virus-infected macrophages. Macrophages may release

oxygen-bearing radicals to which oligodendrocytes, being rich in iron, are particularly sensitive.²⁸⁵

When fetal or postnatal brain tissue is dissociated and put into culture, a significant population of macrophages can be demonstrated. These cells have many features of a monocyte-macrophage lineage, including the expression of myelomonocytic antigens, which may be undetectable *in situ*.²⁸⁶ These macrophages will ingest particulate matter and, having Fc receptors, phagocytose opsonized erythrocytes.^{287,288} It is impossible to state which of the intrinsic brain macrophage populations these cells represent, but microglial cells are the most numerous. Interestingly, if organotypic brain cultures are induced to demyelinate, much of the phagocytic activity is performed by astrocytes.²⁸⁹ This might suggest that the intrinsic brain macrophages have been exhausted or lost from the culture and that, in the absence of blood monocytes to replenish them, have their histiocytic functions taken over by other cells. Myelin phagocytosis by astrocytes *in vivo* has often been described.

MICROVASCULATURE

Capillary vessels in the CNS are specialized by virtue of the blood-brain barrier that maintains homeostasis within the tissue.²⁹⁰ For glucose and neutral fatty acids, which are both required by the CNS, there are carriers for transport across the capillary wall.²⁹¹ Anatomically, the barrier is identified with the endothelial tight junctions, but functionally it may be multifaceted. Many enzymes have been identified in CNS vascular endothelia, which probably constitute part of the barrier to chemical agents.^{292,293}

In areas of malacia (particularly in gray matter), capillary blood vessels respond by endothelial swelling and hyperplasia (Fig. 1-14). Early or focal lesions can often be identified microscopically because such vessels are more prominent than in unaffected areas. There is commonly also the impression of capillary proliferation (sprouting), with increased numbers of straight or branched vessels. Whether or not this is true replication is controversial. Capillary endothelial swelling is seen in other disorders such as viral encephalomyelitides.

In contrast to many extraneural tissues, areas of CNS necrosis and liquefaction do not heal by vascular proliferation and fibroplasia (granulation tissue), and so a cyst or cavity remains (Figs. 1-15 and 1-16). Fibrosis is generally uncommon within CNS parenchyma unless it is from the extension of a severe meningeal lesion or following traumatic implantation of meningeal stroma into the brain or spinal cord. In some chronic disorders, such as prolonged spinal cord compression, vascular adventitial fibrosis can be seen extending into the tissue.

IMMUNOBIOLOGY AND IMMUNOPATHOLOGY OF THE CENTRAL NERVOUS SYSTEM

A question that has fascinated investigators for decades is the issue of communication between the immune system

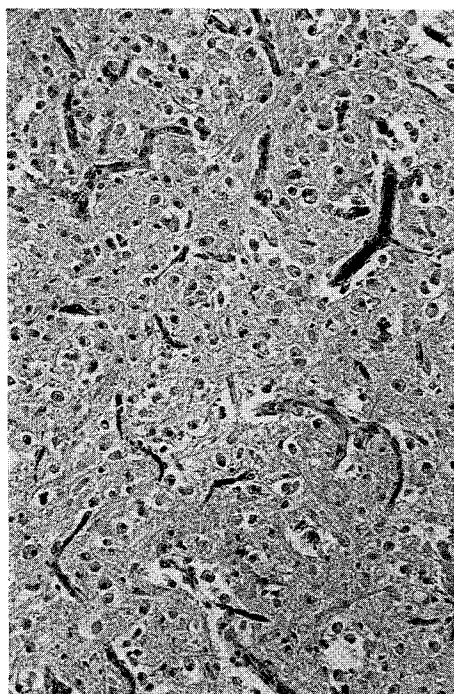


Fig. 1-14. Prominent capillary vessels suggestive of sprouting in an area of poliomyelomalacia, goat. (H&E, ×140.)

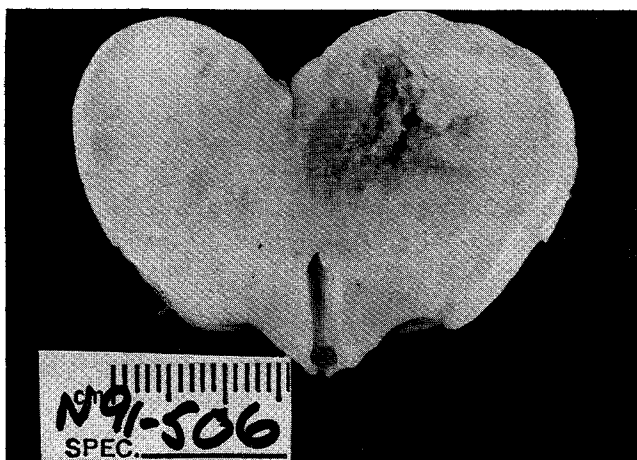


Fig. 1-16. Necrosis (malacia) resulting in cavitation. Thalamus, calf.

and the CNS: What do these two systems know of each other?²⁹⁴ Several lines of evidence suggest that a two-way relationship exists.

1. In 1964 Reif and Allen²⁹⁵ described Thy-1 antigen in mice, which is common to the brain and lymphoid organs. Now it is known that a number of shared antigenic determinants exist between hemopoietic cells and normal or neoplastic neural cells.²⁹⁶
2. Experimental lesioning of the hypothalamus has transient effects on immune responses, including in-

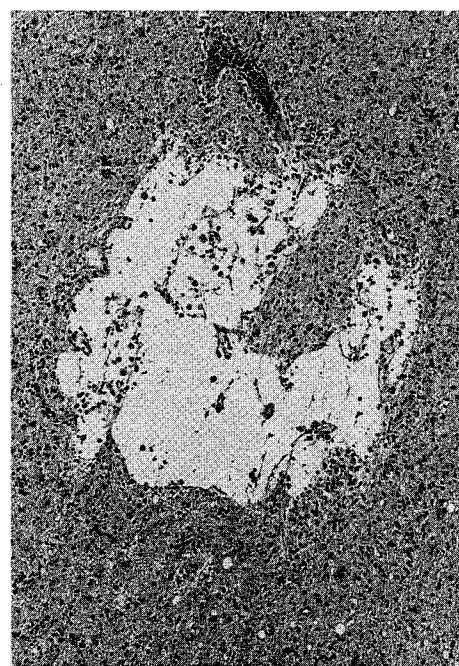


Fig. 1-15. Necrosis resulting in cyst formation. Cerebrum, dog. (H&E, ×90.)

creased splenic suppressor macrophage activity and diminished natural killing,^{297,298} suggesting a capacity for neural modulation of immune function.²⁹⁹

3. Lymphoid organs (lymph nodes, spleen, thymus) and bone marrow are innervated by sympathetic nerve fibers, and immune cells have receptors for chemical neurotransmitters and hormones.²⁹⁴
4. Exposure to foreign antigen results in increased firing rates in ventromedial neurons in the hypothalamus.²⁹⁴

We now realize that a number of spontaneous neurological disorders in animals are **immune-mediated diseases**. Some are triggered by infection with exogenous viruses such as visna, caprine arthritis encephalitis syndrome (CAES), and equine infectious anemia lentiviruses. Immune-complex disease may involve the capillary tuft of the choroid plexus as commonly as the renal glomerulus and is seen in systemic lupus erythematosus in humans and mesangioproliferative glomerulitis in sheep. There are receptors for the Fc component of IgG and for C3b in the choroid plexus.^{300,301} High-avidity IgG-Fc receptors have a periventricular distribution³⁰² that may be of relevance to the periventricular white matter lesions in human multiple sclerosis, visna in sheep, and CAES in goats. In humans, shared antigenicity between tissues is demonstrable in some syndromes such as in patients with gammopathies whose circulating immunoglobulins lead to demyelinating neuropathies and a depletion of peripheral blood natural killer cells.³⁰³

A massive literature has accrued over decades of investigations addressing the area of CNS autoimmune disease and, in particular, myelin sheath and oligodendrocyte injury. This is the legacy of EAE, arguably the best model of the

human demyelinating disease multiple sclerosis. In contrast, autoreactivity to other components of the CNS has received relatively little attention. Serum from patients with motor neuron disease may bind to neurons,³⁰⁴ and antibodies to the neuronal cytoskeleton have been demonstrated in patients with kuru and Creutzfeldt-Jakob disease.³⁰⁵ It can be shown that astrocytes expressing MHC class I antigens are susceptible to cytotoxic T lymphocytes.³⁰⁶ Astrocytes transplanted to the anterior chamber of the eye become inflamed if EAE is induced in the recipient, and they may be an unrecognized target for attack in autoimmune CNS disease.³⁰⁷

APPROACHING NEUROPATHOLOGY

To function at a professionally acceptable level, the neuropathologist needs to understand the principles of clinical neurology and to be reasonably well versed in neuroanatomy. Professional practice is best performed in collaboration with a veterinary neurologist, but this is not possible in all circumstances. Accordingly, the pathologist must be able to determine from the clinical history and neurological examination whether to focus on and sample some or all of the following: the brain, spinal cord, peripheral nerves, neuromuscular junctions, and skeletal muscles. The lack of this ability is probably the main factor leading to poor-quality neuropathological studies in domestic animals. The neuropathologist should use the data from the history, physical examination, and ancillary procedures (such as CSF analysis) to formulate an anatomical diagnosis and then the differential diagnosis, as would a clinician. This allows for the best-informed approach to the necropsy. Second, a sound knowledge of the major structural features of the brain and spinal cord is essential. Experts will have an anatomist's knowledge of brain structure, but this is not necessary to be functional.

When studying a neurological case at necropsy or microscopically, the neuropathologist has to keep in mind a few important principles.

1. Necrosis of neurons in the ventral horn of the spinal cord will produce degeneration in the associated ventral spinal root (Fig. 1-17) and denervation atrophy of muscles that it innervates. Both the neuropathy and the muscle atrophy can be observed at necropsy. In animals born with arthrogryposis, joint fixation is usually due to failure in the development or destruction of motor neuron pools in the spinal cord.
2. Degeneration of axons in ventral spinal roots usually results in chromatolysis in their cell bodies (the axonal reaction) in the ventral horn of the spinal cord, especially in young animals.
3. Necrosis in the internal capsule will result in Wallerian degeneration in the corticospinal projections (Fig. 1-18). This will result in atrophy of the ipsilateral crus cerebri and pyramid, and degeneration of the contralateral corticospinal tract in the lateral funiculus. The latter degeneration will be limited to a few cervical



Fig. 1-17. Slight darkening of spinal ventral roots (*arrow*) reflects Wallerian degeneration. The primary lesion was a protozoal myelitis, which destroyed the ipsilateral ventral horn neurons. Horse.

spinal cord segments in the larger domestic animals, where this tract is short.

4. Compression of the spinal cord that results in axonal interruption will produce Wallerian degeneration in all ascending pathways cranial to the lesion (dorsal columns and spinocerebellar tracts) and in all descending pathways (such as the lateral and ventral corticospinal, tectospinal, vestibulospinal, and reticulospinal) caudal to the lesion. In contrast, the presence of Wallerian degeneration in the dorsal columns alone suggests the probability of degeneration and/or inflammation in the spinal ganglia or dorsal spinal roots (Fig. 1-19).
5. Because demyelinating lesions spare axons, they do not result in Wallerian degeneration in the distal projection of the fiber. Thus demyelination of a dorsal sensory root will not result in Wallerian degeneration in the dorsal funiculus of the spinal cord cranial to the lesion. Because the thoracic spinal cord lesions of Afghan hound myelopathy are myelinolytic, they are not associated with Wallerian degeneration in the cervical or lumbar segments.
6. Cerebellar cortical hypoplasia or degeneration results in shrinkage of the middle cerebellar peduncle, which can be detected as a reduction of the transverse fibers of the pons on the ventral brain stem (Fig. 1-20).
7. Finally, pathologists must remember that in disease, cell or tissue dysfunction typically occurs well in advance of altered morphology.

References are on p. 55.

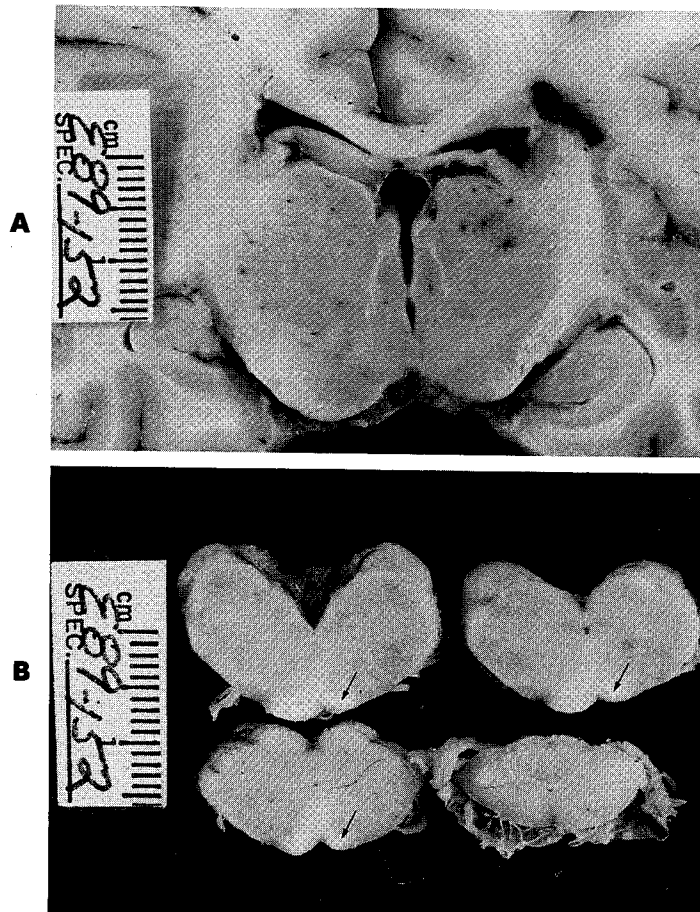


Fig. 1-18. Hemorrhage transects internal capsule, Malayan sunbear (A), resulting in unilateral pyramidal tract atrophy (arrows) (B).

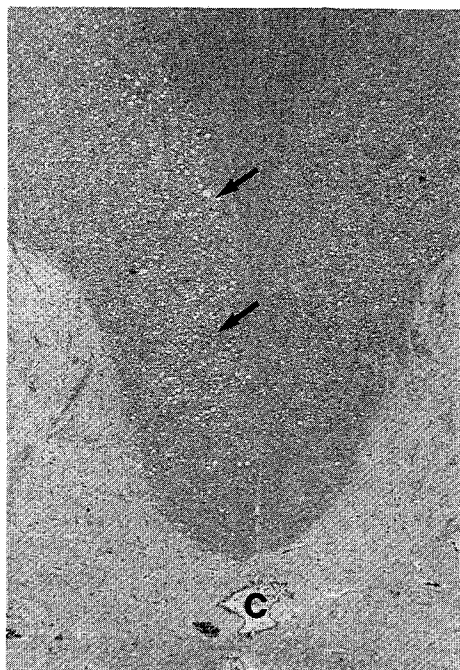


Fig. 1-19. Unilateral dorsal root radiculitis resulted in Wallerian degeneration in the ipsilateral dorsal funiculus (arrows); C, central canal. (H&E, $\times 35$.)

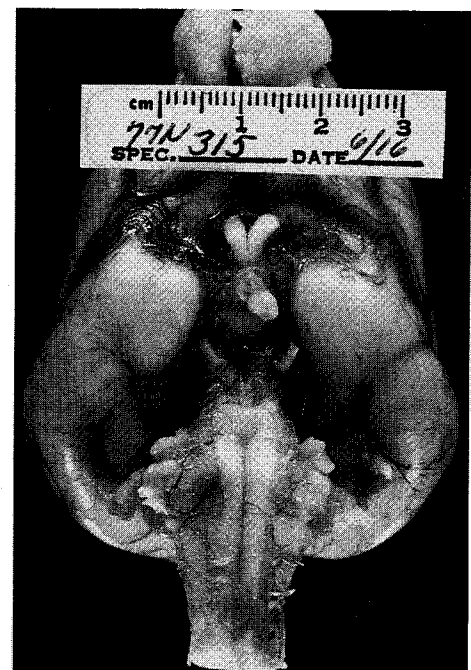


Fig. 1-20. Cerebellar hypoplasia in a dog has resulted in failure of the transverse fibers of the pons to form.

Examination of the central nervous system

Introduction
 Fixation for electron microscopy
 Histochemistry and immunohistochemistry
 Molecular biology
 Tissue culture
 Normal features and artifacts
 Diseases without lesions

INTRODUCTION

The inaccessibility of the central nervous system is a significant deterrent to its routine examination in the course of a necropsy. Our college policy is to remove the brain at all necropsies; once this procedure becomes routine practice, it seems to be less onerous. The calvaria can be cut with a hand saw in large animals and a smaller hand saw or an oscillating saw for small animals. In suspected rabies cases, the calvaria should be opened in a laminar flow hood, and an electrical saw, which can aerosolize tissue, should not be used. With dogs and cats, some pathologists prefer to remove the calvaria piecemeal with bone rongeurs, which ensures minimal trauma to the brain. The dura should be incised bilaterally over both cerebral hemispheres, the tentorium cut deep in the transverse fissure, and a dural incision continued over the cerebellum to the caudal medulla. The exposed brain is removed by transecting the caudal medulla, tipping the cranium caudally to allow access to the olfactory bulbs, which are cut flush with the ethmoid bone, and then sequentially sectioning the paired cranial nerves and the internal carotid arteries.¹ With the brain removed, the empty cranium is examined for evidence of hematomas, fractures, parasites, and masses; for example, nasal carcinomas invade through the cribriform plate in dogs and cats,² and ocular squamous cell carcinomas in cattle may infiltrate the cranium along cranial nerves.³ Osteochondroma may involve the cranium in dogs,⁴ sometimes compressing the underlying brain. The sella turcica should be examined for inflammatory or neoplastic lesions. If of potential interest (rabies, herpesvirus encephalitis), the trigeminal ganglia can be harvested. In appropriate cases, the eyes should also be collected, and vestibular disorders require an examination of the bullae and fixation of the inner ear in the petrous temporal bone.

The spinal cord should be removed in all cases of CNS disease, even though clinical signs may be referable only

to the brain. In small animals this can be accomplished by performing a dorsal laminectomy. Once performed, the spinal cord should be removed by holding the dura with forceps and sectioning the spinal roots as close to the intervertebral foramina as is possible, thus collecting the spinal ganglia. Once removed, the dura should be carefully incised longitudinally to facilitate fixation. For large animals, the vertebral canal can be opened in routine cases by a parasagittal approach with a band saw. In suspected cases of equine cervical stenotic myelopathy, it is informative (if time and inclination permit) to disarticulate the cervical vertebrae individually. After removal of the spinal cord, the vertebral canal should be visually examined and palpated for protruded disks, displaced fractures, and vertebral and epidural masses. Extradural lymphoma (most common in the cow and the cat) can be mistaken for epidural fat; if there is doubt, a stained impression smear will settle the issue.

The pathologist may wish to consider radiographing the intact vertebral column before beginning the dissection if this was not done during life and a malformation, luxation, or fracture is suspected. Fixation of the spinal cord in Zenker's fixative will render some soft tissue lesions detectable by radiography.⁵

The intact brain should be examined for evidence of swelling and herniation (see section on cerebral edema in this chapter), meningeal opacity and exudate, malformation, masses that may be extramedullary or intramedullary, and focal or multifocal lesions that may range from infarcts to granulomas to metastatic tumors. Comparing the size and symmetry of both halves of the cerebrum often identifies a mass or other lesion evident only after brain cutting. Palpation of the unfixed brain, if not done to excess, is permissible. Areas with acute necrotizing lesions may be soft (malacic), whereas low-grade astrocytomas or old inflammatory lesions can be firmer than the normal tissue (sclerotic). If brain injury has left a residual cyst, the tissue is focally fluctuant and yielding. In severe hydrocephalus or hydranencephaly, the cortical mantle is appreciably thinned and the brain fluid-filled. It is important to examine for the absence of normal structure such as congenital optic nerve hypoplasia or an acquired pyramidal atrophy secondary to a motor cortex or internal capsule lesion. In contrast to the close inspection of the cerebral vasculature given in human neuropathology, it receives scant attention in veterinary neuropathology, and routinely opening the basilar vessels may

be worthwhile. The spinal cord with dura reflected is examined for abnormalities such as discoloration, swelling, or areas of compression.

The brain and spinal cord should be fixed by immersion in at least 10 times their volume of 10% buffered formalin for a minimum of 2 to 3 days and preferably at least a week. Some pathologists make a transverse incision in the cerebrum to the level of the lateral ventricles or sagittally through the corpus callosum to aid penetration of the fixative, but this is optional rather than obligatory. The spinal cord (with dura opened) should be straight and can lie flat or be suspended vertically in fixative. Fixation for EM is discussed later in this section.

After fixation and then examination of the intact brain, the whole brain should be sectioned in the transverse plane (about 0.5-cm-thick slices), the pieces laid out sequentially from rostral to caudal, and examined carefully for abnormalities. The sectioned brain may reveal obvious lesions, but some require the trained eye of experience. Viral infections produce the least in the way of gross changes, with some exceptions, such as caprine arthritis encephalitis in goats, canine distemper, and equine herpesvirus type 1 vasculopathy. Hemorrhage and edema often cause swelling that displaces the midline toward the unaffected or less affected side. Lesions in white matter are often yellowish brown or gray. Periventricular lesions produce a noticeable thickening and nodular irregularity of the ependymal surfaces, as in feline infectious peritonitis encephalitis and some forms of protozoal encephalitis in dogs. Meningoventricular inflammatory lesions often involve the choroid plexuses, which are noticeably thickened. Destructive lesions obliterate normal architecture, as in Pug dog encephalitis, wherein the junction of cerebral cortical gray matter with its underlying white matter is lost. Cerebrocortical necrosis, sometimes with laminar cavitation, is often obvious in a case of bovine polioencephalomalacia of more than 3 or 4 days' duration. Primary tumors (most are gliomas) vary from poorly demarcated focal expansion of the tissue to discrete and often soft or hemorrhagic foci, the latter more characteristic of high-grade gliomas. Metastatic tumors may be few or numerous, for example, malignant hemangioendothelioma (hemangiosarcoma). Parasite tract lesions are characterized by their continuity over several segments of the brain and are usually hemorrhagic. Spinal cord lesions show the same spectrum of changes as in the brain, and the tissue is examined by making multiple transverse sections. If these sections are limited to the spinal cord and do not cut the dura, the segments remain suspended in the dura in their normal anatomical relationship.¹ This is useful for segment identification if repeated studies are necessary.

Some changes have a characteristic pattern that can be anticipated; for example, aqueductal obstruction from malformation, inflammation, or compression produces hydrocephalus of the lateral and third ventricles. Extensive de-

generation of motor neurons in the spinal cord results in a tan or brown discoloration of the ventral spinal roots from Wallerian degeneration and a yellow discoloration of skeletal muscle from denervation atrophy in the field of innervation. Cerebellar atrophy results in shrinkage of the transverse fibers of the pons. In other diseases, the lesions have a specific topography, but it is unique; for example, in selenium toxicity in pigs, destructive lesions involve the lateral portions of the ventral gray column and are confined (in the spinal cord) to the cervical and lumbar enlargements.

The medical neuropathologist is a trained specialist whose work is usually limited to this system in a single species. In veterinary medicine, there are relatively few pure neuropathologists, and most animal neuropathology is conducted by generalists. To function adequately, a comprehensive although not exhaustive knowledge of neuroanatomy is essential. The pathologist will be aided by routinely processing the same areas of the brain, which will provide familiarity with the architecture and composition of these regions. Where questions arise such as to the normal numbers of neurons in particular nuclei or the density of myelinated fibers, comparison with tissue from a normal, age-matched control is the most satisfactory.

Brain areas with obvious lesions can be trimmed for sectioning. In the absence of any recognized abnormality, sections from six to eight brain areas should be sampled, for example, frontal lobe, level of optic chiasm, occipital lobe, thalamus, rostral colliculus, cerebellum through the cerebellar peduncles, and caudal medulla. Two or three transverse and longitudinally oriented sections of each region of spinal cord (cervical, thoracic, lumbar, and so on) should be taken. The longitudinal section can be taken in a number of ways, the choice depending on the element of greatest interest (gray or white matter). Our routine procedure is to take a parasagittal section in the vertical plane through the dorsal and ventral gray columns. Equally, the section can be taken horizontally, through the dorsal gray columns, central canal, or ventral gray columns. In a few diseases, examination of specific areas of the neuraxis is useful or even crucial, although the majority of neurological disorders encountered in animals are more or less diffuse in their manifestations. If necessary, it is usually possible to return to the sectioned brain and trim in specific areas, especially if the initial brain removal and cutting have been done with care.

Diseases that result in brain hypoxia or energy deprivation produce lesions in the caudal colliculi. Specific diseases and their lesions include yellow-star thistle poisoning in horses (globus pallidus and substantia nigra), multisystem neuronal degeneration in Cocker Spaniel dogs (basal nuclei, brain stem nuclei), swayback in lambs (brain stem nuclei), trapezoid body in Afghan dog myelopathy, and the nucleus of the dorsal spinocerebellar tract in equine degenerative myeloencephalopathy.

FIXATION FOR ELECTRON MICROSCOPY

The method chosen for fixation of the nervous system will depend on the nature of the case at hand. For light microscopic examinations, immersion fixation into large volumes of 10% buffered formalin provides perfectly acceptable fixation, provided there is minimal delay between death and the necropsy. Whether for the CNS or the PNS, perfusion fixation is the optimal procedure if electron microscopic study is planned. However, this is often impractical or impossible, as unfixed specimens may also be required for microbiological, biochemical, or other examinations. Immersion fixation of 2- to 3-mm-thick brain or spinal cord slices into EM fixative, such as Karnovsky type solutions of glutaraldehyde and paraformaldehyde, will provide acceptable preservation. The specimens should be harvested with the fewest possible number of incisions of the fresh tissue, as this will produce pressure artifacts. Blocks can be trimmed after an initial period of fixation. One option is deep anesthesia of the animal and a craniotomy. Samples of fresh brain can be taken as needed and then the animal perfused for EM examination.

There are several options for vascular perfusion, and each laboratory needs to establish its own preferred protocol by trial and error. The fixative can be delivered passively by gravity feed (particularly if the volume is relatively small, such as that needed for laboratory animals) or by a peristaltic pump or other mechanical system.⁶ To avoid tissue damage, it seems prudent to maintain the delivery force at no greater than systolic blood pressure (approximately 120 mm Hg). Some investigators prefer to deliver a preperfusion wash such as physiological saline or Ringer's solution through the vascular system; others begin directly with the fixative. Heparinization (100 to 400 IU/kg) may aid the procedure,⁷ and heparin can be included in the anesthetic or the flushing solution. A relatively large caliber catheter should be used to deliver the solution, and it can be inserted into the left ventricle or the proximal aorta. As soon as delivery begins, the right auricle must be incised to allow for escape of the blood-fixative mixture. The nature of the fixative⁸ is another choice; 3% glutaraldehyde or 1% glutaraldehyde–1% paraformaldehyde (Karnovsky's type solution) are commonly employed after being buffered to physiological pH and chilled. In the latter, the tissue can remain in the fixative for several hours without detriment. The volume required will vary from 2 to 4 L for a cat or a dog to 10 to 40 L for a large animal. Blanching of the mucosae or yellowing from glutaraldehyde, muscle contractions, and stiffening with extension of the limbs and jaw rigidity are signs that the perfusion is proceeding well. Sporadically one finds at the completion of the procedure pink soft areas of the neuraxis that have not been adequately perfused, perhaps because of vasospasm. After perfusion, artifactual changes such as dark neurons can be minimized by leaving the tissue in situ for at least 1 hour and preferably longer (3 to 4 hours).⁹

In diagnostic neuropathology, there often is no alternative than to process formalin-fixed nervous tissue for EM.¹⁰ The quality of the end product is variable and will be worthless if autolysis is advanced. Then again, this will often yield usable specimens, although structural artifacts (such as splitting or ballooning of myelin sheaths) will be more pronounced than in optimally prepared tissue. However, we have examined the ultrastructural features of numerous neurological cases where only formalin-fixed tissues were available. Most often, useful data result, sometimes of quality acceptable for publication.

HISTOCHEMISTRY AND IMMUNOHISTOCHEMISTRY

The history of the development of special staining techniques for the various elements of the nervous system is an account of the evolution of neuropathology as a discipline. Because these histochemical stains were employed only on nervous tissue, neuropathology emerged as a somewhat exclusive club within the field of pathology with a language only its members could use and enjoy. Perhaps this attitude exists somewhat to this day.

Routine neuropathological cases can be adequately evaluated with H&E stain. It is important for trainee pathologists to learn to recognize the range of microscopic changes in diseased CNS tissue with this basic tool. If particular elements of the tissue warrant further inspection, appropriate special techniques can be employed. Luxol fast blue (LFB) stains the proteolipid protein in myelin sheaths and is used to evaluate myelin development and integrity. LFB is usually combined with a counterstain, either cresyl echt violet or PAS. Some laboratories combine LFB with an axonal stain.¹¹ Silver impregnation techniques stain the axonal cytoskeleton and so show the presence and shape of axons. They are useful in presumed demyelinating diseases (to confirm that axons are preserved), in axonopathic disorders such as neuroaxonal dystrophy, and in Wallerian degeneration. Holmes or Romanes stains are commonly used in veterinary medicine; Bodian, Bielschowsky, and Glees techniques in human neuropathology.^{12,13} The suppressive Nauta-Gygax technique (Fig. 1-21)¹⁴⁻¹⁶ is somewhat paradoxical in that it stains only degenerate axonal fragments, whereas modifications of this technique selectively stain degenerating boutons.¹⁷ The Golgi stain has had wide application in neuroanatomy and is particularly useful to reveal structural changes in neuronal processes; it is amenable to light or electron microscopy.^{18,19} Astroglial cells were traditionally demonstrated by Cajal's gold sublimate method, but this has given way to the ease, convenience, and attractive results that ensue from GFAP immunohistochemistry. No reliable histochemical (or other) markers exist for mature oligodendrocytes in tissue. Myelin sheaths can be shown by LFB and by virtue of their myelin antigens by immune techniques. The Marchi technique to selectively

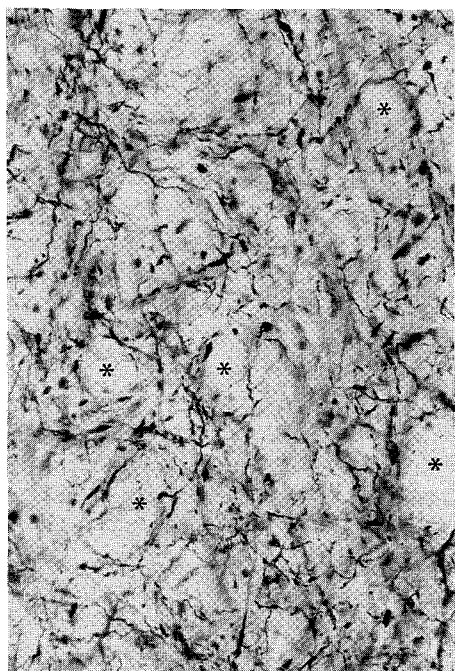


Fig. 1-21. Nauta-Gygax technique showing preterminal degeneration of axons in the lateral geniculate body, sheep. Asterisks indicate the position of neuronal cell bodies. ($\times 560$.)

stain degenerate myelin in frozen sections is less widely used now. Microglial cells have traditionally been demonstrated by the silver carbonate procedure. The delicate staining of the processes of these cells is subtle and requires some experience for this evaluation. They can be demonstrated by lectin binding (for example, *Ricinus communis* agglutinin-1) and with some antibodies. Some histochemical procedures have specific usefulness; for example, Lafora bodies are PAS positive, as are the macrophages in globoid cell leukodystrophy. Gram stains are useful in bacterial infections, and Gomori methenamine silver in fungal diseases.

In evaluating young animals for possible hypomyelination, the concurrent study of an age-matched normal animal is always helpful, especially if the patient is less than a month of age. Because these diseases usually spare peripheral myelin, it is useful to compare the myelin-staining density in cranial or spinal nerves (which should be normal) with that within the CNS in sections of the tissue. Very often the observation of diminished LFB staining is equated with the presence of demyelination. Too commonly such is not the case, as in an area of trauma, infarction, or Wallerian degeneration, where myelin loss is not associated with axon sparing. The identification of axonal integrity can be difficult in paraffin-embedded tissues. It is most favorably shown in sections cut parallel to the direction of tracts. Axonal integrity is evaluated much more satisfactorily in 1-micrometer-thick sections of plastic-embedded tissue, which can also be pursued ultrastructurally. One-micrometer sections of osmicated specimens are good for assessing hypomyelinating states.

The development by Sternberger of immunocytochemical techniques that can be readily applied to formalin-fixed and paraffin-embedded tissue specimens added a new dimension to a number of morphological sciences. In neurobiology, they have found a place in studies of neural development and cell differentiation, neuroanatomy, neuroendocrinology, and neuropathology. Immunocytochemical techniques have facilitated investigations ranging from disordered myelinogenesis, axonopathic diseases, infectious disorders, storage diseases, diseases of aging, and neoplastic disorders (Fig. 1-22). Immunocytochemistry has been extended from light to electron microscopic procedures and has been combined with in situ hybridization. New equipment allows for automated immunohistochemistry, permitting the ready use of many reagents on single or multiple cases.

This new tool has also been employed in veterinary medicine in studies of spontaneous and experimental nervous system disorders. The most routinely employed reagents are antisera or monoclonal antibodies to glial fibrillary acidic protein, neurofilament and the other intermediate filaments, S-100 antigen, Leu 7, neuron-specific enolase, and myelin basic protein, although there are many more that, more or less, have a place. Many commercial reagents are marketed for use on human tissues and so must be tested and validated for animal specimens. In general, most work well on animal tissues with a few notable exceptions; for example, epithelial membrane antigen is a marker for perineurial cells in humans but not in animals. The use of immunocytochemistry in human neuro-oncology has gained great popularity in the last 15 years. This tool has not proven to be the definitive procedure for the diagnosis of CNS tumors as was perhaps at first anticipated. Immunocytochemistry should be viewed as at best providing some general guidelines, as Rubinstein has said, "Signposts—not markers—in neural tumour differentiation."²⁰

MOLECULAR BIOLOGY

The 1980s were distinguished by the furious pace of developments in molecular biology. Following the evolution of immunohistochemistry and monoclonal antibody technology during the prior decade, a variety of techniques emerged that permit the identification, amplification, and quantification of DNA and RNA in tissues and tissue extracts. These new tools (such as immunoblotting, hybridization techniques, and the polymerase chain reaction) have important applications in studies of infectious diseases, genetic disorders, and neoplasia in a clinical setting and in the laboratory. Medical pathologists (including neuropathologists) have been quick to incorporate these tools into their daily practice, attesting to the immense value of this new technology.²¹⁻²⁶ Modifications have allowed the use of colorimetric rather than radioisotope probes for in situ hybridizations, which renders the technique much more appealing as a routine diagnostic procedure. Results can be obtained within a working day,²⁷ and the procedure can be automated

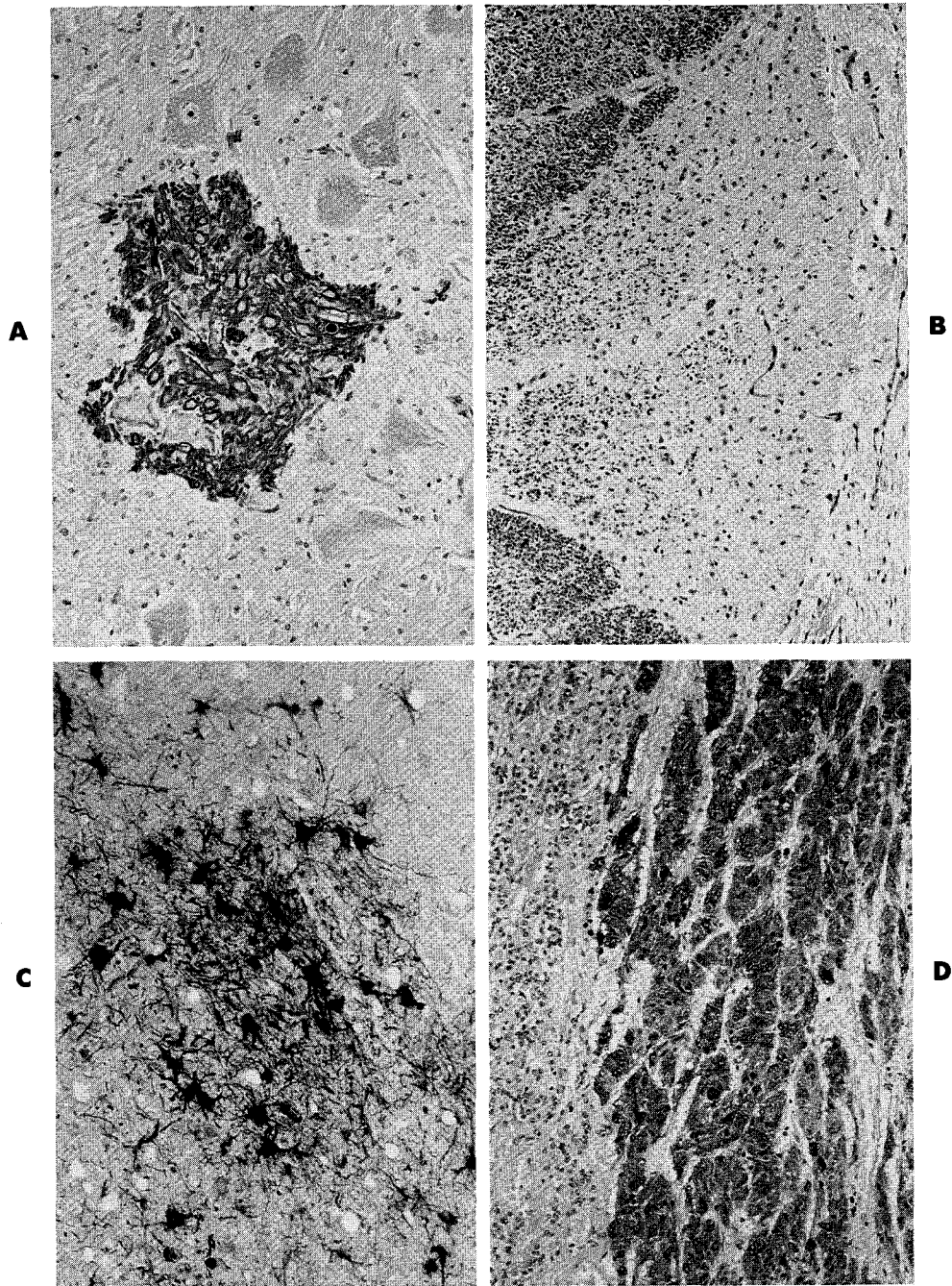


Fig. 1-22. Immunocytochemistry. **A**, Spinal cord anomaly, foal, with Schwann cells populating the spinal cord and producing peripheral nerve myelin. Antibody to P₀ protein. ($\times 140$.) **B**, Congenital axonopathy, calf. Neurofilament antibody shows paucity of axons in the fasciculus gracilis. ($\times 140$.) **C**, Canine distemper virus-infected glial cells in the medulla of the cerebellum. Monoclonal antibody to viral nucleocapsid. ($\times 140$.) **D**, Tumor of pituitary (pars intermedia), horse, contains ACTH. ($\times 140$.)

and paired with immunocytochemistry.²⁸ It is now possible to probe the molecular basis of genetic defects and the abnormal gene products. In neurology, for example, this has led to important advances in our knowledge of the myelin proteins of the central and peripheral nervous systems in health and disease.²⁹⁻³² Examination of restriction fragment length polymorphism is an important tool for screening for genetic disease³³ including several important human neurological disorders.³⁴ Studies of oncogene expression are contributing to neuro-oncology,^{35,36} and finally the development of transgenic animals offers enormous potential for studies in many diverse areas of biomedical research.³⁷

The application of these new tools is gradually appearing in veterinary medicine, particularly in microbiology. Evidence of their use in neurology can be found in studies of viral diseases of the CNS by nucleic acid hybridization³⁸⁻⁴⁰ and by PCR.^{41,42} Screening for carriers of genetic mutation by PCR has been reported (for example, bovine citrullinemia).⁴³ Doubtless this is just the tip of the iceberg in terms of what is to follow, for certainly the practice of all branches of medicine will change drastically with this revolution in molecular biology.

TISSUE CULTURE

Tissue culture techniques have found wide application in many fields of neuroscience. In areas relevant to neuropathology, these include the characterization of CNS tumors in culture, studies with infectious agents in cultured primary CNS cells or cell lines, and studies of the effects of humoral (serum-derived) cytotoxic factors on constituents of the CNS, as well as studies of the growth, development, and differentiation of normal neuroectodermal cells. Many growth factors with trophic effects on cells of the CNS, such as epidermal growth factor and fibroblast growth factor, have been examined and their effects defined in tissue culture studies. The pioneering work of Raff and his collaborators has made important contributions to our knowledge of oligodendrocyte and astrocyte differentiation, based in large part on *in vitro* studies. Bornstein and Raine and many other investigators have published extensively on the pathogenesis of experimental autoimmune encephalomyelitis and multiple sclerosis, using organotypic cultures of CNS fragments maintained in Maximow chambers.⁴⁴⁻⁴⁶ Other options are to work with dissociated brain cultures, popularized by McCarthy and de Vellis, or with rotating aggregating cultures, which, like the Maximow product, recapitulate normal organ structure.

NORMAL FEATURES AND ARTIFACTS

With a secure knowledge of the normal structure of a tissue and the artifactual changes to which it is prone, the recognition of pathological change is easy. Although this statement is trite, it remains valid to this day for the nervous system. There are a number of "nonlesions" that the embryonic pathologist must learn to recognize, for it is common

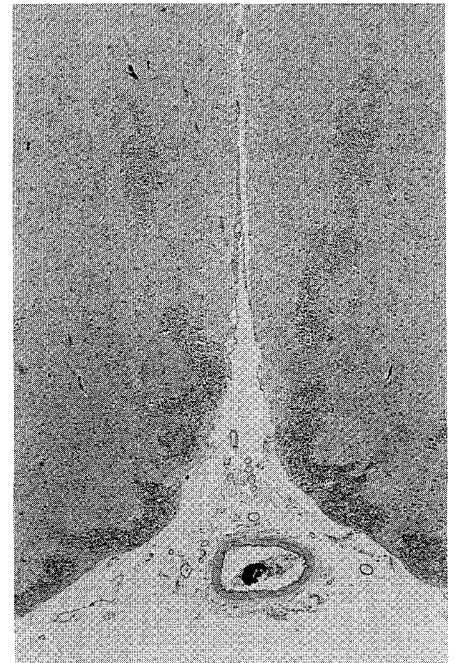


Fig. 1-23. Normal extension of subependymal cells (from adjacent to the lateral ventricle) into the olfactory cortex. Ferre (H&E, $\times 35$.)

practice to interpret these (microscopic) features as abnormal and potentially significant for the case at hand. Many nonlesions are conspicuous populations of germinal cells that can be found in the neonate or even throughout the whole life span in the normal brain and spinal cord.

1. The **external germinal cells** of the cerebellar cortex. These small cells can be found below the pia mater in the first 1 to 2 months of postnatal life or longer in some species (calves). They are programmed to migrate through the molecular layer, past the Purkinje cells, and into the granule cell layer. Consequently they slowly become dissipated in the first weeks after birth. They should not be misinterpreted as non-suppurative meningitis.
2. The **subependymal plate**, most prominent about the lateral and ventral aspects of the lateral ventricle: contains the remnants of the germinal zone of the primitive neural tube. These cells can be recognized by their small, round nuclei with dense particulate chromatin. This population of small, primitive cells persists throughout life. Occasionally a transverse section through the frontal lobe contains a nest of small cells within the white matter. It is usually a pocket of the subependymal plate about the rostral extensions of the lateral ventricle. Normally a central ring of ependymal cells can be found within the cellular focus. These germinal cells also accompany the extension of the lateral ventricle through the olfactory

peduncle to the olfactory bulb, which is present in all animals but best developed in large animals where the lumen is patent. Remnants of subependymal germinal cells are often relatively prominent about the aqueduct in foals up to a few months of age. They may be found in a perivascular location (presumably migrating) that creates the impression of a perivascular cuff. Characteristically, they form an eccentric aggregate around the blood vessel, rather than a complete circumferential collar typical of that seen in an inflammatory reaction. Similar germinal cells are found permanently as nests within the olfactory cortex (Fig. 1-23), which is not organized into the six laminae of the neocortex but represents the phylogenetically older paleocortex and has fewer layers with one prominent, somewhat undulating lamina of neurons. All of these features are often less confusing if the whole brain can be sectioned and the bilateral symmetry appreciated. With the contemporary tissue-processing systems employed in many laboratories, this is generally not an option.

Whether these germinal cell rests are reservoirs for neurons that die throughout life is unknown. In some avian species, there is evidence for neuronal replacement in adult life. Germinal cell populations are thought to give rise to some intracranial tumors, such as the cerebellar medulloblastoma from external germinal cells and periventricular gliomas from the subependymal plate.

Other structures to be familiar with are the circumventricular organs.

1. The **subcommissural organ** is a local modification of ependymal cells below the caudal commissure that projects into the aqueduct. These are tall, columnar ependymal cells involved with aldosterone production.
2. The **area postrema** of the caudal medulla is located dorsal and slightly lateral to the parasympathetic nucleus of the vagus. It is a cluster of small capillaries and glial cells that underlie a layer of flat ependymal cells and may appear to be a reactive focus. It is an area where the blood-brain barrier is open. Various functions have been attributed to it, including chemoreception, neurosecretion, and control of numerous visceral activities.

Other normal features include the following:

1. In some areas of the CNS neurons normally appear centrally chromatolytic, including the olivary nucleus (Fig. 1-24), pontine and supraoptic nuclei, and the lateral cervical nucleus in the spinal cord.
2. Neurons with cytoplasmic vacuoles in the red nucleus of cattle are normal. In sheep, vacuolated neurons are found at low frequency in the medulla.⁴⁷
3. Axonal spheroids and vacuoles in the lateral cuneate nucleus of the medulla are common, especially in the aged, but have been seen in foals.

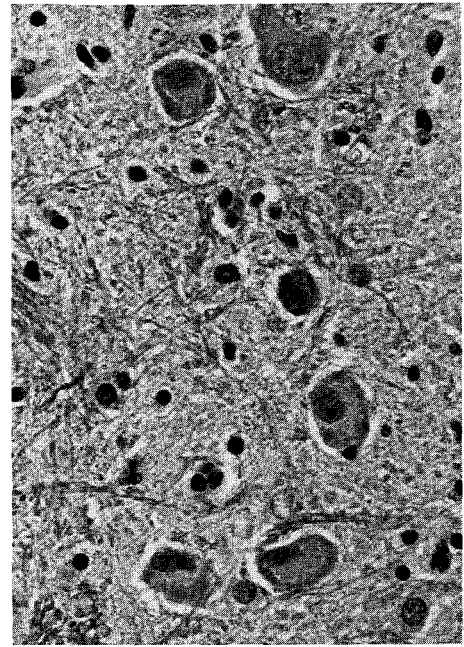


Fig. 1-24. Olivary nucleus, dog. Some neurons appear to show central chromatolysis but are normal for this nucleus. (H&E, $\times 560$.)

4. It is normal and of no pathological importance to observe a short segment of oligodendrocyte-produced myelin extending into the proximal segment of a cranial or spinal nerve root.
5. There is a normal variation in the number of satellite cells around neurons in the cerebral cortex. It varies with the different regions of the neocortex and between species. They are always very abundant in spinal and trigeminal ganglia.

The brain of neonatal domestic animals is histologically immature for the first month or so of life. The cerebrum is highly cellular, with the framework of the layered neocortex evident but many neurons still small. The white matter is poorly myelinated and so is pallid microscopically and has the appearance of increased cellularity. An evaluation of the neonatal CNS for hypomyelination often requires a normal age-matched control brain for comparative purposes. At the other end of life, there is sometimes an impression of gliosis in gray matter areas such as the cerebral cortex and the thalamus due to the prominence of neuronal satellite cells. Particularly in the deep laminae of the neocortex, the numbers of satellite oligodendrocytes may seem to be increased. The pathologist should resist the interpretation of satellitosis until the satellite cells form a continuous ring and there is evidence of degenerative changes in the neuronal soma. Other changes in the neuraxis that are associated with aging are discussed in the section in this chapter on this topic.

Melanin deposits can be found in the leptomeninges in

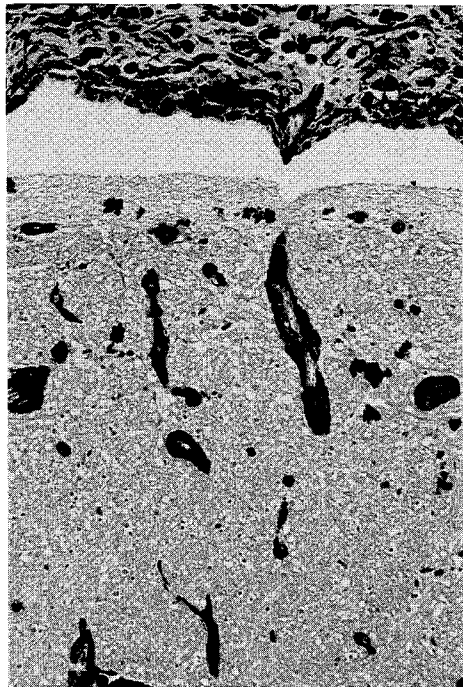


Fig. 1-25. Melanocytes in the leptomeninges and perivascular spaces. Normal sheep, medulla. (H&E, $\times 140$.)

animals with brown or black hair coats and regularly in sheep (Fig. 1-25). Pigmentary deposits are found in melanocytes in the leptomeninges, in the stroma of the choroid plexus, and about blood vessels that course into the parenchyma. In sheep this may form an impressive aggregate, histologically resembling a neoplasm. Beware of melanin in immunocytochemical studies of the CNS, as the pigment can mimic the chromogen diaminobenzidine. Melanin-laden cells appear in both the positive and negative preparations. **Neuromelanin** normally accumulates as fine brown granules in the cytoplasm of certain neurons, most conspicuously in the hypothalamus and pars nervosa of the pituitary, but is demonstrable elsewhere.⁴⁸ In humans, sufficient neuromelanin is present to produce grossly visible pigmentation in the substantia nigra and the locus ceruleus. The pigment is distinct from melanin and is a product of catecholamine metabolism. Ultrastructurally, neuromelanin closely resembles lipofuscin granules.^{49,50}

The CNS is susceptible to some **artifacts** that affect all tissues, and it also has a repertoire of its own. Artifactual alterations to gray matter can simulate the effects of trauma and hypoxia, whereas vacuolar change in myelin may mimic intramyelinic edema or Wallerian degeneration. In deciding whether the tissue change is genuine or bogus, the neuropathologist should draw on the history and clinical course of the patient's illness as well as the pathological examination. The most useful feature is evidence of a response to the putative injury, for example, vascular endothelial swelling, the influx of neutrophils into sites of early de-

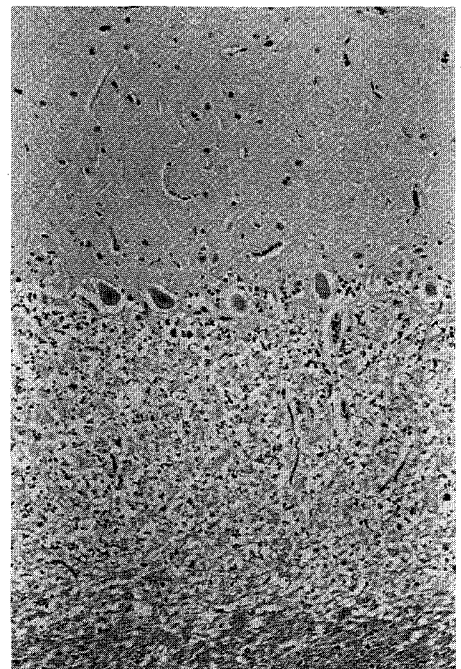


Fig. 1-26. Autolysis of granule cell neurons, cow. Note relative preservation of Purkinje cells. (H&E, $\times 140$.)

generation, and macrophages within myelin digestion chambers. On longitudinal sections, continuous chains of myelin swellings usually indicate a lesion and often disclose macrophages within the ballooned sheaths. Most difficult is the interpretation of noninflammatory white matter vacuolar change. Generally such lesions affect the tissue with bilateral symmetry but are often more severe in some white matter areas than others, although there are exceptions. In contrast, postmortem myelin vacuolation is seen as a fairly widespread, uniform fine vacuolation of the tissue. Mild swelling of astrocytes in gray matter and condensation of the nuclei of glial cells may help to confirm a suspicion of autolysis.

Occasionally stains or slide adhesives become contaminated with microorganisms (often yeasts) that may be deposited in the tissue. We have seen examples that closely mimic clusters of protozoan organisms and that can be particularly confusing if the tissue reaction is inflammation. Sometimes the deposits of pseudo-organisms can be found in the slide beyond the confines of the tissue. If in doubt, recut the block and prepare fresh solutions. Freezing tissues produces crystals that are seen as linear fissures in the tissue, whether CNS or other. In autolyzed CNS, glial cells appear small and hyperchromatic such that many more glia than normal resemble oligodendrocytes. The cerebellar granule cell layer is particularly prone to postmortem lysis in the cow and other bovidae (Fig. 1-26). Characteristically, the Purkinje cells above the depleted granule cell zone are relatively well preserved. With autolysis, swelling of astroglial

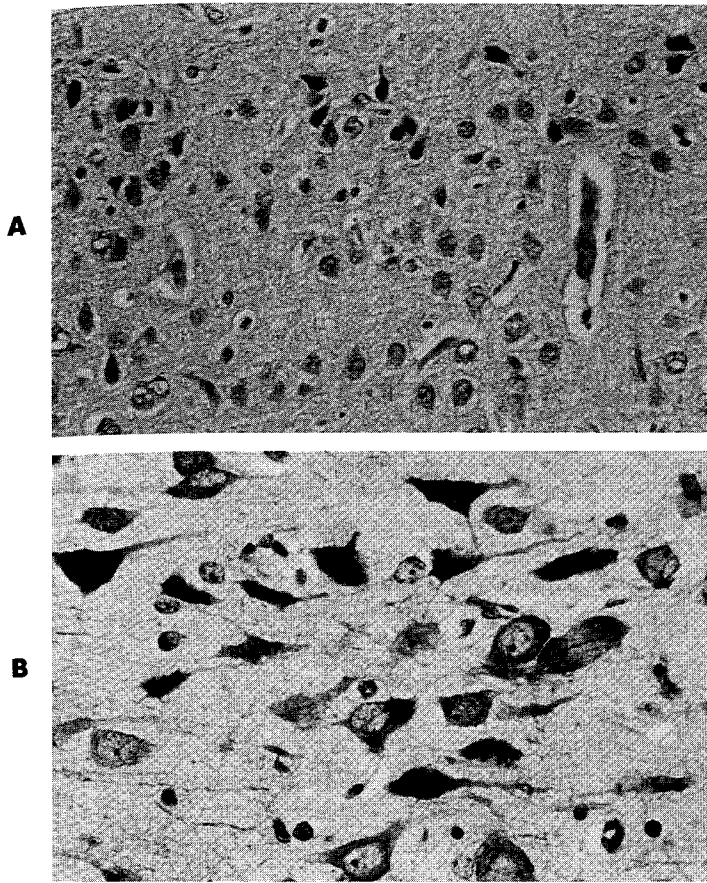


Fig. 1-27. Dark neurons. **A**, Dark neurons in lamina one of cerebral cortex, rat. (H&E, $\times 350$.) **B**, Dark neurons in cerebrum, pig. Note that many neurons appear normal. (Luxol fast blue, cresyl echt violet, $\times 560$.)

cell processes about Purkinje cells can give the false impression of a lysosomal storage disease affecting these cells. As this autolytic process advances, a line of separation appears in the cerebellar cortex at the level of the Purkinje cells, separating the molecular layer from the granule cell layers. With postmortem autolysis, the CNS imbibes fluid from the extracellular compartment and is prone to liquefaction. If microscopic examination is crucial, fixation in a corrosive solution such as Bouin's fixative will appreciably harden the tissue and sometimes yield sections of surprising detail.

When the brain and spinal cord have been removed at autopsy, they should be examined for gross lesions. Areas that may appear to be necrotic are appreciably soft to palpation. Excessive handling of the unfixed brain should be avoided as it produces **dark neurons**. Simply fixing neurosurgical biopsy specimens by immersion in formalin, removing the brain of a normal animal immediately after death and immersing in fixative, or the immediate removal of a perfused brain from the skull can induce dark neurons.⁵¹ In affected neurons, both the nucleus and the cytoplasm shrink and stain deeply (Fig. 1-27). There is slight contracture of

the neuronal cell body from the neuropil, dense basophilic staining of the cytoplasm usually obscuring the nucleus, and a corkscrew-shaped apical dendrite.^{52,53} Characteristically, a single or a few dark neurons are seen within an otherwise normal-appearing population, and their recognition as a nonlesion is not difficult. These cells sometimes are slightly eosinophilic and may be a source of confusion with respect to ischemia. Perineuronal spaces are usually less frequent than in ischemia. At the ultrastructural level, the Golgi complex may be expanded and electron lucent. Mitochondrial expansion does not occur, and swollen astrocytic processes rarely contact these perikarya. Dark neurons are more abundant over the crests of the cerebral gyri and cerebellar folia, whereas ischemic cell changes are commonly (but not exclusively) found at the base of the sulci.

Optimal preparation of nervous tissue is by perfusion fixation followed by a delay of several hours before the brain and spinal cord are removed. Immediate handling of the CNS even after perfusion will produce a few dark neurons.⁵³ If avoidance of the dark neuron artifact is crucial, Cammermeyer⁹ has devised an effective, two-step perfusion protocol for light microscopy. The first solution (which contains gum acacia, sodium chloride, and formalin) is a flush and is followed by a second that is a modified Heidenhain's fixative. Cammermeyer describes how the volume of the perfusate is calculated, based on body weight. Brain removal should be delayed for 4 hours.

Cerebellar cortical Purkinje neurons have a propensity to simulate ischemic cell change, but in most cases it is artifact. If genuine, such cells are slightly condensed, elongated, and brightly acidophilic, and the nucleus is pyknotic. Only rarely is this genuine, for example, in the very early stages of some canine cerebellar cortical abiotrophies, perhaps reflecting the action of an excitotoxin. Small gaps in the Purkinje cell layer are normal, whereas pathological loss of Purkinje cells is marked by a proliferation of astrocytes (Bergmann glia) at the junction of molecular and granule cell layers.

Because the nervous system is rich in lipids, processing through solvents for paraffin embedding will produce fine vacuoles in white matter, especially if the tissue undergoes autolytic change before fixation. Holding trimmed CNS tissue for 48 hours in alcohol may introduce a vacuolar artifact predominantly in white matter (corona radiata of cerebrum, corpus callosum, cerebellar medulla).⁵⁴ **Mucocytes** (Buscaino bodies) are a rare artifact in white matter that manifest as pale, blue-gray, amorphous bodies (Fig. 1-28). They are PAS positive and metachromatic and seem to arise by an unusual reaction between the fixative solution and myelin. Dissolution of these bodies may occur, leaving the white matter spongiotic.

DISEASES WITHOUT LESIONS

Part of the appeal for studying the nervous system is that disordered structure and function are highly correlated. This

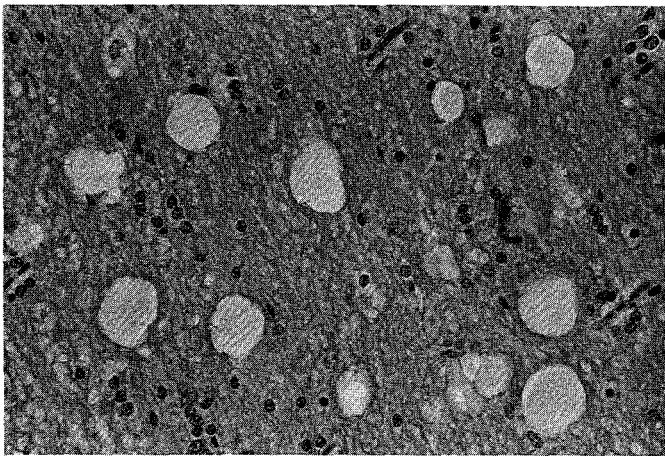


Fig. 1-28. Mucocytes, dog. Cerebral white matter. (H&E, $\times 350$.)

allows the clinical neurologist to define a regional basis for the abnormalities detected—an anatomical diagnosis—from which one proceeds to the most likely etiological diagnosis consistent with the patient's signalment, history, and clinical findings (including ancillary procedures such as CSF analysis and imaging techniques). The veterinary pathologist who is routinely faced with cases of neurologic disease will benefit greatly from close interaction with the clinical neurologist, including the observation of the clinically affected patient. Needless to say, the benefit works in both directions and will materially aid the clinician in reaching the most appropriate diagnosis. Neuropathologists must

bear in mind that some clinical disorders are mediated without structural change in tissues; such disorders include those of the neuromuscular junction (myasthenia gravis, botulism), tetanus and other neurotoxicities (strychnine, metaldehyde), idiopathic epilepsy and metabolic derangements (hypocalcemia, hyperkalemia), and, less commonly, hyponatremia.⁵⁵ For these diseases, other approaches to diagnosis must be pursued, as conventional morphological studies, ranging from gross to ultrastructure, will be inconclusive.

At times, morphological changes are found in areas of the brain that do not account for the deficits shown by the patient. Such changes include (1) incidental changes such as a healed infarct or an old parasite lesion or (2) secondary changes in the brain produced by the disorder. As an example of the latter scenario, the syndrome of hereditary quadriplegia and amblyopia in Irish Setter dogs is marked by the absence of neuropathological changes, apart from the rare case that shows ischemic change in cerebellar Purkinje cells, which may be secondary to seizures.⁵⁶ Seizures may be a fairly common cause of neuronal degeneration. Some disorders of the human nervous system result from the distant effect of tumors—so-called **paraneoplastic syndromes**—and these are many and diverse.^{57,58} For example, cerebellar degeneration occurs in some patients with pulmonary, ovarian, and other tumors, apparently related to the generation of anti-Purkinje cell antibodies. Ganglionitis and peripheral neuropathies have been associated with a variety of tumors and there is some evidence for their occurrence in animals, discussed in Chapter 7.

References are on p. 61.

Cerebral edema and brain swelling

The escape of fluid in abnormal quantities from the circulation into interstitial tissue spaces or the failure of normal recirculation of tissue fluids results in **edema**. Severe brain edema is potentially life-threatening because of the limited ability for accommodation of increased volume (tissue or fluid) within the confines of the dura and the cranium. When the brain is severely swollen, something has to give.

In the CNS, there are factors that bear on the formation of edema fluid that differ from extraneural sites. The CNS parenchyma does not possess a lymphatic system, and the interstitial space between cells, especially in the gray matter, is much narrower than in other tissues. When CNS edema develops, of necessity it largely accumulates within cells, although interstitial fluid will form if cells lyse or if the edema is severe. The CNS capillaries have several important features. Vessel density is not homogeneous; gray matter

areas with neuronal somata and dendritic zones have the highest density of capillary blood vessels. Capillary vessels of the CNS are devised to minimize fluid transport from the circulation into the tissue. Where contiguous endothelial cells abut, fusion of the outer leaflets of their plasma membranes form **tight junctions** (zonulae occludentes), the structural basis for the blood-brain barrier. The formation of these endothelial junctions is induced by astrocytes whose end feet encircle the vessel, closely apposed to the capillary basal lamina. This property of astrocytes can be demonstrated by transferring these cells to the anterior chamber of the eye; any capillaries in the iris that are colonized by astrocytes will develop similar tight junctions.¹ Except for specialized areas of the neuraxis that have a secretory neuroendocrine function (e.g., the pineal, hypothalamus, and area postrema) and the choroid plexus (which forms CSF),

the capillary vessels are not fenestrated. Endothelial pinocytotic activity, which delivers fluid from the vascular lumen to the abluminal surface, is much less conspicuous in the CNS than in other tissues. Connective tissues (collagen and reticulin) are relatively sparse about most brain capillaries and venules, which may render them prone to injury. The CNS parenchymatous arterioles and venules have a perivascular space, but this is obliterated around capillaries. However, in the brain stem and spinal cord,² capillary vessels and venules have a perivascular space between the endothelial cell or pericyte and the glia limitans containing collagen fibrils.

Cerebral edema probably develops to some degree in all pathological states, whether degenerative or inflammatory disorders, traumatic injuries or neoplasia. The recognition of cerebral edema at necropsy may be straightforward or very difficult. CNS edema affects both gray and white matter but the latter more severely. Edema around chronic, focal lesions such as abscesses, parasitic cysts, and primary or metastatic tumors in white matter often produces dramatic swelling,^{3,4} particularly if the centrum semiovale is involved. The brains of fetal and neonatal animals are normally softer and wetter than those of more mature animals and can be difficult to evaluate for cerebral edema unless it has resulted in blatant herniation.⁵ The same caution must be applied to necropsies where the postmortem interval is prolonged, as imbibition of tissue fluid and plasma results in mild brain swelling after death. The use of excessive pressure during perfusion of the CNS can produce tissue disruption and edema.

At necropsy, pulmonary edema can be recognized because the lung is wet, firm, and heavy. Although comparable evaluations can be made of the brain, we are more dependent upon recognizing brain edema by its effects on the organ. The gross appearance of cerebral edema depends on its cause, severity, and duration. Moderate to severe edema causes brain swelling (Figs. 1-29 and 1-30) that may be evident as flattening of the cerebral cortical gyri and slight narrowing of sulci. Cerebral hemispheric swelling compresses the underlying brain stem, flattening the rostral colliculi and distorting the aqueduct. Areas of hemorrhage (so-called Duret hemorrhages) may be found within the brain stem. These changes are best demonstrated in transverse sections of the brain. As the swollen brain expands and fills the confines of the calvaria, some regions are prone to herniation. If this occurs, the accompanying blood vessels are likely to become occluded,⁶ which may result in hemorrhage or infarction. Commonly with brain swelling, the caudal lobe of the cerebellar vermis protrudes as a flattened lip over the medulla oblongata toward the foramen magnum. Petechial or small ecchymotic hemorrhages are frequent in the displaced vermian lobe and/or in the underlying compressed medulla. The rostral portion of the vermis may herniate into the brain stem, which is displaced caudally with brain swelling.⁶ Herniation of the median aspects of

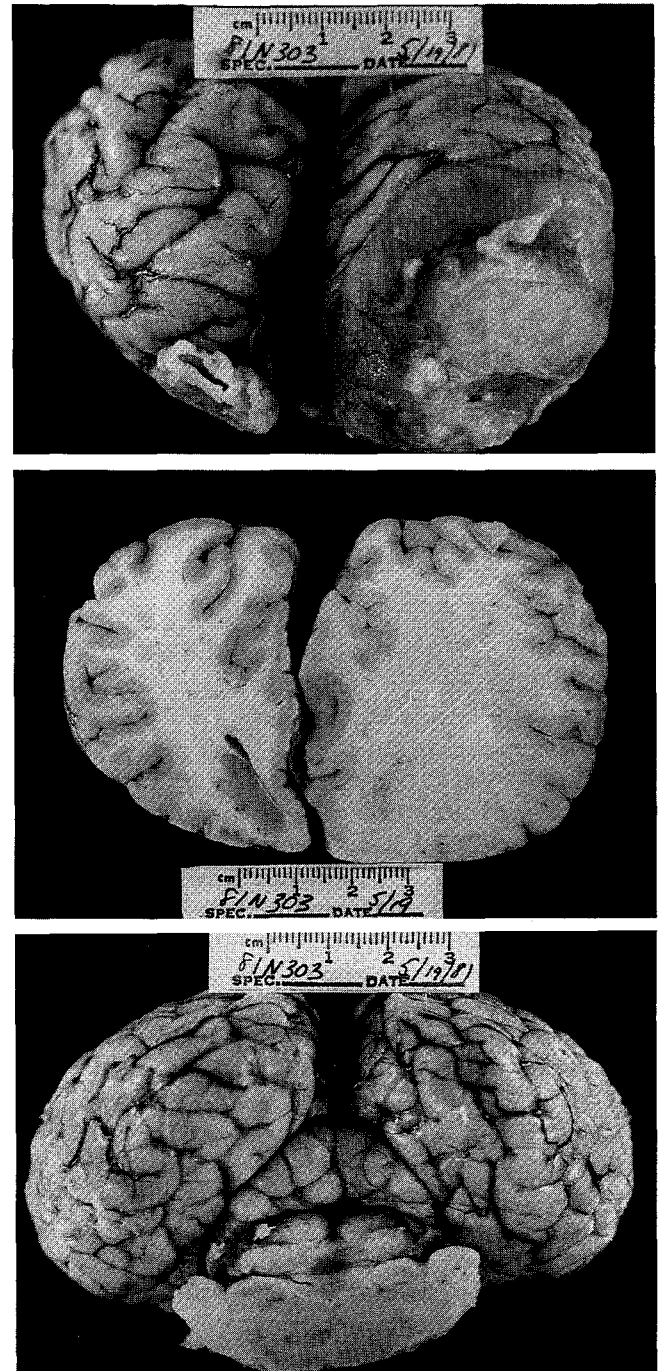


Fig. 1-29. Brain swelling. **A**, Granuloma of frontal lobe, horse. **B**, This resulted in marked cerebral edema (prominent in the white matter), leading to subtentorial herniation and brain stem compression, **C**.

the occipital cortex (mainly the parahippocampal gyrus) beneath the tentorium cerebelli is common in moderate to severe cerebral edema. When the brain is removed from the cranial cavity, the diagonal groove produced by the tentorial notch is clearly evident. Unilateral cerebral hemispheric

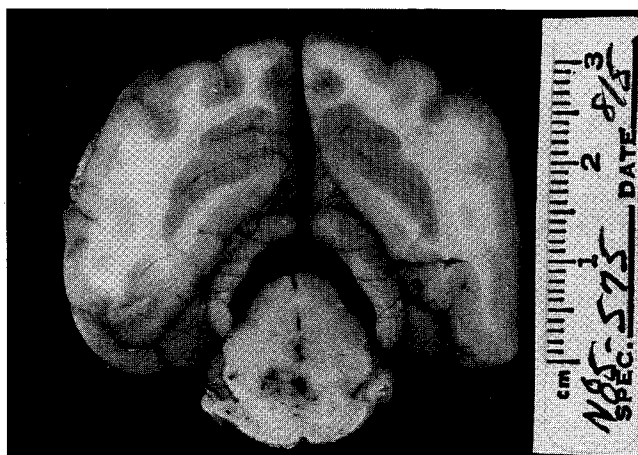


Fig. 1-30. Brain swelling in a dog resulted in herniation, constricting the colliculi and producing deep brain stem hemorrhage.

mass lesions may produce swelling sufficient to displace the cingulate gyrus beneath the falx cerebri toward the unaffected hemisphere.

When the brain is sectioned, edematous swelling of white matter becomes evident. If asymmetrical, there will be a midline shift toward the less affected or unaffected side. Edematous brain is never exceptionally moist but may be slightly wet and soft, and sometimes the white matter is yellowish. It may appear normal in texture or even slightly dry in chronic cases. In cases of cerebral edema that are limited to gray matter areas, for example, in bovine citrullinemia, the extent of edema is typically milder, and gross brain swelling may not be evident.⁷

Of attempts to explain the development of brain edema, the pathogenetic scheme devised by Klatzo^{8,9} is most widely accepted. In **vasogenic edema** the primary insult is to the wall of cerebral blood vessels, allowing the escape of plasma fluid and proteins under the hydrostatic pressure of the circulation. The inciting vascular injury may be brain or spinal cord trauma, vasculitis, so-called mass effect (a neoplasm or other mass), or a cerebrovascular accident. It has been observed that in some chickens, natural exposure or inoculation with Marek's disease herpesvirus induces depression and recumbency 9 to 12 days after exposure. The disorder is named **transient paralysis**, and most birds recover in 1 to 2 days from what is believed to be an encephalopathy resulting from vasogenic edema.^{10,11}

Vasogenic edema predominantly affects white matter, where fluid accumulates within the cytoplasm of astrocytes and spreads in the interstitial spaces. The dense meshwork of gray matter neuropil is effectively resistant to interstitial white matter edema that stops at gray-white junctions. Arterial blood pressure influences how far edema fluid will

spread in white matter and lowering systolic pressure will diminish fluid spread. Vasogenic edema moves over very long distances and from one hemisphere to the other via the corpus callosum. A chronic epidural abscess involving the frontal lobe can produce sufficient brain swelling from vasogenic edema to induce herniation of the occipital cortex beneath the tentorium cerebelli. The herniation may be bilateral, although most severe ipsilateral to the abscess. In humans it is recognized that chronic leukoedema can result in myelin degeneration,¹² but this is rarely if ever recognized in animals, as its development may take many months.

Microscopically, the recognition of vasogenic edema may be difficult and its limits hard to define. There is an impression of pallor to the tissue with routine H&E or myelin stains. Free interstitial fluid is not normally evident except in the most severe cases, wherein eosinophilic lakes will be seen. Acute edema in white matter causes swelling and necrosis of astrocytes and hypertrophy of surviving cells, which proliferate and produce abundant fibrous processes. Acute swelling of oligodendrocytes is less conspicuous and may be a postmortem change. In humans, it is noted that junctional (arcuate) fibers are more resistant to the development of edema than those central in the corona radiata; this may be the case in animals but has not been recorded.

Chemical mediators that may act on the cerebral microvasculature (opening the blood-brain barrier) and contributing to tissue injury in vasogenic edema have been scrutinized. These include oxygen-free radicals,¹³ glutamate and arachidonic acid metabolites,^{14,15} bradykinin, and histamine.¹⁶

Cytotoxic edema results from an injury to a glial cell that disturbs osmoregulation of that cell (depletion of energy stores and failure of energy-dependent ionic pumps). This leads to the cell swelling with fluid, and in this regard cytotoxic edema differs from edema in other tissues in which the fluid accumulation is interstitial. Vascular integrity remains intact or is only altered very subtly, perhaps to allow increased transudation of fluid across small vessels. Conventional measures of blood-brain barrier integrity, such as by trypan blue injection, indicate that the barrier is intact. Cytotoxic edema reflects a specific cellular insult and may result from ischemia and/or hypoxia, nutritional deficiency, an intoxication, or an inherited metabolic disorder. Cerebrocortical astrocyte swelling in bovine citrullinemia and myelin sheath swelling in bovine maple syrup urine disease are examples of cytotoxic edema of the last category.

Brain swelling from cytotoxic edema is less dramatic than that seen with vasogenic edema. It may affect just gray matter, just white matter, or both. Grossly, the brain may be appreciably swollen and displaced, or it may appear normal. Microscopically, cytotoxic edema results in astrocyte swelling, which in gray matter is conspicuous in the end feet of perivascular and perineuronal astrocytes. Where cytotoxic edema affects oligodendrocytes, it produces a

spongiotic appearance in the white matter due to intramyelinic edema with splitting of myelin sheaths. Sometimes the outer oligodendrocyte mesaxon swells, whereas expansion of the cell soma is very limited. In cytotoxic edema, fluid but not plasma protein escapes, its accumulation is limited to intracellular sites, and the extracellular compartment is not enlarged.

Vasogenic edema often results from a local injury, whereas cytotoxic edema is commonly mediated by a global disorder. Some forms of CNS injury must act on both elements, that is, producing both vascular and glial injury concurrently. It has been argued that the separation of brain

edema into vasogenic and cytotoxic types is arbitrary and should be unified into a single mechanistic concept reflecting varied perturbations of cerebral endothelial metabolism.¹⁷ Other classifications would separate brain swelling into that resulting from (1) increased volume within the vascular compartment, (2) cellular swelling, or (3) extracellular edema. Thus the periventricular edema associated with hydrocephalus, which first expands the interstitial spaces of brain parenchyma, would qualify as one form of the third category.¹⁸

References are on p. 62.

Inflammation of the central nervous system

Hallmarks of CNS inflammation
 Demyelination
 Infectious agents and CNS inflammation
 Neuroinvasiveness and neurovirulence

HALLMARKS OF CNS INFLAMMATION

The inflammatory reaction is a host defense mechanism, acquired and refined through the millennia of evolution. Inflammation is never a primary event; it is a reaction to local injury that may range from trivial to life-threatening. In all inflammatory diseases, the reaction itself contributes something to tissue damage, reaching its most dramatic expression in the immunopathological disorders¹ in which there is aggressive reactivity to autoantigens or to exogenous agents that in themselves may be inconsequential pathogens.

The inflammatory process has several components that come into play in an orderly sequence. Early events are marked by the escape or active egress of blood constituents—fluid, electrolytes, proteins, leukocytes—into tissues and the activation of important mediators including the acute phase proteins, the complement cascade, the coagulation pathway, and fibrinolytic systems. Inflammation also has proliferative components that involve the vasculature, connective tissues, and parenchyma of the organ. A mixing of exudative and proliferative reactions occurs over the course of the inflammatory process, depending on the virulence of the causative agent and the host's response to it. Bacterial

leptomeningitis in neonates is marked by the outpouring of fibrin-rich fluid and polymorphonuclear leukocytes into leptomeningeal and ventricular compartments. This is often lethal because of brain swelling and subsequent brain stem compression before the acute inflammatory changes have progressed further. Other CNS inflammatory diseases are typified by hypertrophy or proliferation of glial elements—specifically, microglia and astroglia—and perivascular cuffing, with minimal effusion of fluid and protein; such characterize the important group of viral encephalomyelitides.

A generic inflammatory response can be described and measured in a variety of extraneural tissues. That which is mounted by the nervous system has some important differences^{2,3} that reflect the unique nature of the tissue. The CNS exists in a somewhat sequestered and immunologically dormant state within the body. Free access of blood constituents to the tissue is dampened by the capillary endothelial blood-brain barrier. The CNS lacks specialized dendritic antigen-presenting cells, and the intrinsic expression by CNS cells of major histocompatibility complex (MHC) molecules, especially class II, is low.⁴⁻⁶ Nevertheless, these features seem to be no impediment to the development of inflammatory processes in the neuraxis. There is no lymphatic system within nervous tissue, but cells and antigens within the CNS drain into the circulation and to the cervical lymph nodes.^{7,8}

The crucial features that are the hallmarks of CNS inflammation are (1) **perivascular cuffing**, (2) **gliosis**, and (3) **neuronal satellitosis and neuronophagia**. Demyelination is a feature of some inflammatory diseases, but they

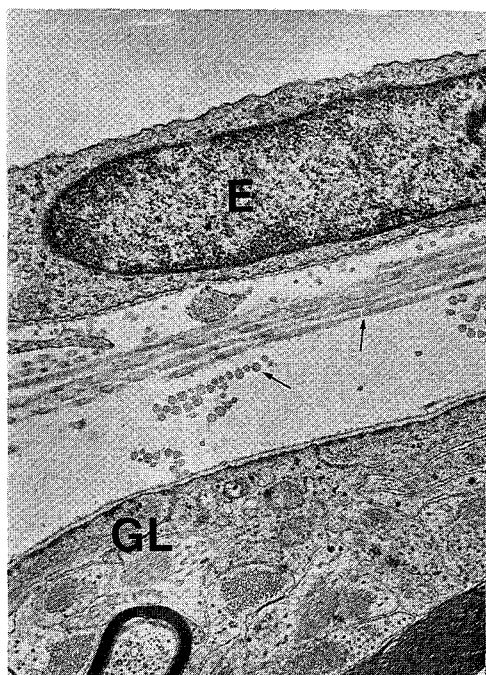


Fig. 1-31. Electron micrograph showing a normal perivascular space containing collagen fibrils (arrows) in the spinal cord. *E*, the endothelial cell; *GL*, glia limitans. ($\times 19,500$.)

are exceedingly few in number. The development of all these changes has relative but not absolute specificity for an inflammatory process. For example, an immunological response will commonly be mounted to a glioma, morphologically evident as perivascular cuffs of lymphocytes about the perimeter of the tumor. Blood monocytes will pour into an area of CNS infarction and slowly depart as debris-laden macrophages (gitter cells). In neither of these two examples would these histopathological findings be interpreted as encephalitis—although this is perhaps a moot point and open to argument.

A perivascular compartment, actual or potential, exists around all CNS arteries, arterioles, venules, and veins. This perivascular compartment is situated between the wall of the blood vessel and the glia limitans, contains CSF, and is generally viewed as continuous with the subarachnoid space. In domestic animals, capillaries in the spinal cord and in some areas of the brain stem also possess a perivascular space (which may contain a few collagen fibrils) (Fig. 1-31), whereas in other areas of the brain the perivascular space around capillaries is obliterated. There is also evidence for ensheathment of blood vessels in the subarachnoid space by pial cells. It is suggested that, on the arterial side, this pial sheath extends into the brain, producing a separate periarterial space.⁹ This pial layer is fenestrated, allowing communication between the periarterial and perivascular spaces.

A characteristic feature of CNS inflammation is perivascular cuffing (Fig. 1-32), the accumulation of leukocytes

of one or multiple types in the perivascular space. The composition of the cuff may vary over the course of the disease and is influenced by the use of some pharmaceuticals. Blood vessels in the CNS parenchyma, meninges, and choroid plexus stroma may all be involved. All perivascular cuffing results in vasculitis of some degree, but it is important to differentiate between innocent migration of leukocytes through the vessel wall and the primary vasculitides.¹⁰ In the latter diseases, the cellular inflammatory response within the CNS is prominently angiocentric and (in contrast) relatively meager within the parenchyma. This is best evaluated by examining sections with the low-power objective of the microscope. Further, if vasculitis is suspected, it should be sought in other organs, for such diseases are frequently generalized.

The orderly extravasation of leukocytes through the blood vessel wall into injured tissue is an essential element of the inflammatory reaction. It signals to the histopathologist that an inflammatory process is in train and says something about the type of inflammation. Leukocyte extravasation en masse requires the generation of chemotactic factors in the injured tissue and the activation of adhesion molecules on circulating leukocytes and vascular endothelial cells. Extravasation first requires leukocyte margination and subsequent attachment to endothelia. This latter process is under precise regulation to avoid the nonspecific adhesion and potential injury to vascular lining cells. Once bound, leukocytes migrate through the vascular wall into the perivascular compartment, which affords access to the tissue. In the nervous system, there is also the opportunity for dispersion of cells in the CSF-filled subarachnoid space, ventricles, and central canal. Accordingly, CSF pleocytosis is an important clue that the neuraxis is inflamed.

The identification and characterization of these adhesion molecules form an active area of biomedical research. Antagonists of these specific ligands may afford a novel approach to the therapeutic control of acute and chronic inflammatory diseases. Important adhesion molecules include the **integrins** (a family of membrane glycoproteins), the leukocyte and endothelial **selectins** (carbohydrate-binding proteins), and the **immunoglobulin superfamily** of adhesion molecules (such as the intercellular adhesion molecule-1, [ICAM-1]), which is expressed by endothelial cells, leukocytes, and other cells (reviewed by Jutila¹¹). Up-regulation or activation of these ligands is triggered by factors present or released at sites of injury, which include antigen and cytokines and lymphokines such as γ -interferon, interleukin 1, and tumor necrosis factor (TNF). Studies have shown a correlation between active inflammation and the expression of adhesion molecules in the CNS in multiple sclerosis and other disorders,^{12,13} and doubtless it will be demonstrated in other encephalomyelitides.

In lymphoid organs such as lymph nodes and Peyer's patches, lymphocytes home to the tissue by the binding of specific lymphocyte ligands to receptors expressed on high

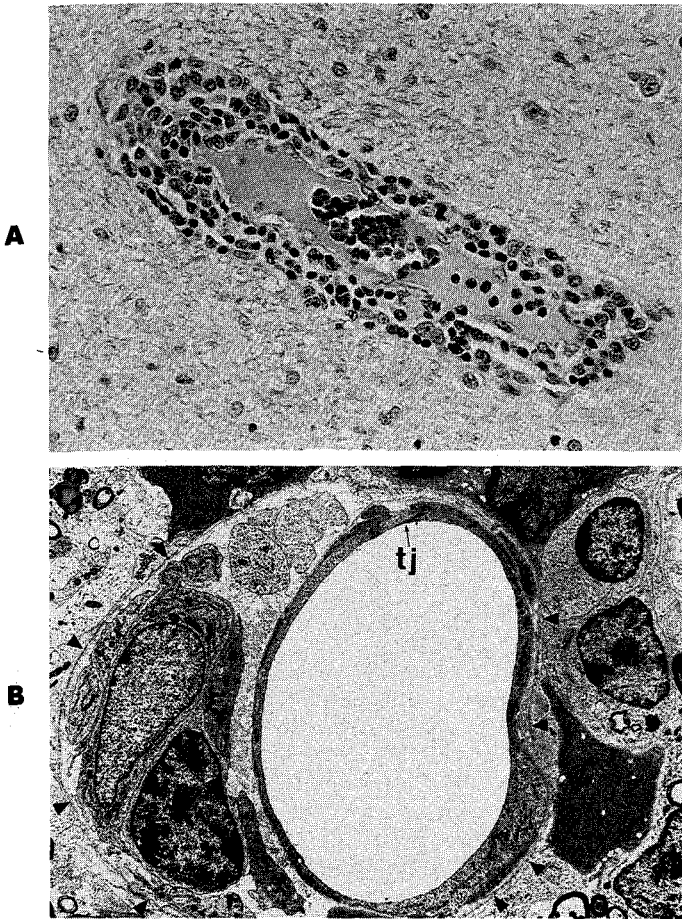


Fig. 1-32. A, Encephalitis, cat. Perivascular cuff of mononuclear cells. Note that a few leukocytes are intravascular. (H&E, $\times 350$.) B, Encephalitis, dog. Electron micrograph of a perivascular cuff of lymphocytes and plasma cells. Arrowheads indicate the glia limitans: To the left of the vessel, leukocytes are in the perivascular compartment. To the right they have entered the parenchyma. Note the endothelial tight junction (tj). ($\times 5600$.)

endothelial venules. Lymphocyte subsets show a difference in their affinity for binding to cerebral microvessel endothelium *in vitro* (e.g., CD8 cells bind more efficiently than do CD4),¹⁴ but a CNS-specific homing mechanism has not been proposed. How are lymphocytes, which are virtually impossible to detect in normal nervous tissue, directed to enter and accumulate in the brain and spinal cord? The initial signal for leukocytes to enter the CNS is unknown⁵ but could come from processed antigen, presented by cerebral vascular endothelial cells to leukocytes in circulation. Alternatively, it has been suggested that small numbers of T lymphocytes *normally* enter and traffic through the CNS, regardless of their phenotype or antigen specificity, if they are in a state of activation.^{4,15,16} T blasts, sensitized to non-neural antigens, will have disappeared in 1 or 2 days, whereas those reactive to CNS antigens persist for a longer

period. These cells release factors into the tissue that up-regulate endothelial ligands and attract further immunocompetent cells, resulting in massive expansion of the pool. From studies of EAE, it has been proposed that many and perhaps the majority of lymphoid cells in perivascular cuffs are recruited nonspecifically and so will not be antigen-specific.¹⁷ Once B or T lymphocytes have extravasated, antigen presentation may be effected by meningeal cells, the perivascular microglia, resident or monocyte-derived macrophages, or perhaps astrocytes.^{18,19}

Most cells in perivascular cuffs are of hematogenous origin, but these are not the sole constituents. The CNS vascular pericytes and cells of the adventitia are capable of rounding up into mononuclear cells that are probably capable of phagocytic activities or antigen presentation. For example, some reports of canine granulomatous meningoencephalomyelitis describe proliferative changes in perivascular reticuloendothelial elements as contributing to the vessel-related lesions.²⁰

Some generalizations can be made with respect to the composition of perivascular cuffs: In bacterial diseases, polymorphonuclear cells predominate with a minor component of mononuclear cells. In fungal infections the proportions are reversed, often with swollen epithelioid macrophages that may harbor the agent of interest. Viral diseases are largely manifest by lymphocyte-rich populations with some plasma cells and monocytes. Some arbovirus infections incite a polymorphonuclear cell response; eastern equine encephalomyelitis is a good example. Immune-mediated disorders are often healthy mixtures of polymorphonuclear and mononuclear cells, particularly if immune complex formation is involved, and plasma cells are often prominent. In thrombotic diseases such as thrombotic meningoencephalitis, vascular occlusion precludes the development of cuffing about many injured vessels.

The fate of cells that constitute the perivascular cuffs is rather poorly understood. Many, such as neutrophils, monocytes, and T lymphocytes, appear to migrate into the tissue to perform their specific functions and probably expire *in situ*. Some, however (such as B cells), may function largely in the perivascular compartment. As inflammation wanes, it becomes necessary to dispose of any redundant inflammatory cells. This probably occurs by programmed cell death or **apoptosis**,²¹ a process infrequently described in the CNS.^{22,23} Tissue debris is slowly removed by macrophages migrating from the parenchymal lesion toward the perivascular or leptomeningeal spaces.

Gliosis (Fig. 1-33) is the increased prominence of glial cells, resulting from cytoplasmic swelling and the acquisition of more cell processes, from cell proliferation, or from both. Gliosis may be **isomorphic**, in which they follow the normal pattern of disposition of glial cells in the tissue (seen in the aging brain), or **anisomorphic**, in which their accumulation is disorderly. The latter is much more common, and an important clue to the microscopist is the de-

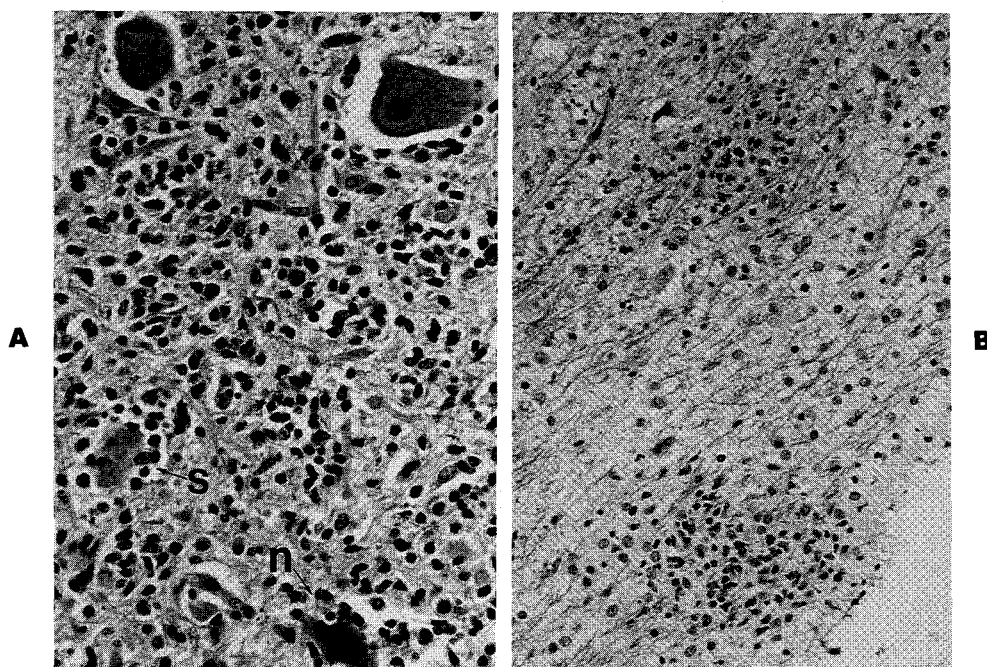


Fig. 1-33. A, Diffuse gliosis, neuronal satellitosis (s) and neuronophagia (n). (H&E, $\times 350$.) B, Focal gliosis. (H&E, $\times 225$.)

tection of discrete areas of the tissue that are inappropriately hypercellular. Very often, what is loosely designated gliosis contains a contribution from both the circulation and endogenous cells.²⁴ Indeed, once lymphocytes infiltrate the tissue, they may be difficult to distinguish from some glial cells. Often the gliotic focus is seen as clusters of naked nuclei of indeterminate cell type, and the nonspecific term gliosis is accommodating.

Potentially either of the macroglia (oligodendrocytes or astrocytes) or microglia may participate in gliosis; by convention, astrocytic reactivity is implied. Proliferation of oligodendrocytes around degenerate neurons may contribute to neuronal satellitosis, and proliferation of these cells within white matter occurs quite early in sites of inflammatory demyelination.²⁵ However, the important players in inflammatory gliosis are microglia and astroglia. Focal proliferation of microglia about the perikaryon of degenerating neurons (microglial "stars") is one hallmark of neuronal diseases. In neurotropic viral infections, their proliferation is often a mixture of focal aggregations and a diffuse infiltration between and among neurons. Reactive microglia have long, slender nuclei that emphasize their rod shape, and *in vitro* data suggest that this is the form of proliferating microglia.²⁶ Microglial cells are also found associated with the cerebral microvasculature. Localization at this site would facilitate recognition of circulating antigen and would allow antigen presentation of lymphocytes.²⁷ An astrocytic reaction is traditionally viewed as a reparative response in the CNS, akin to scarring in extraneural sites. In some viral infections, astrocytic hypertrophy and proliferation are early responses to viral infection of these cells or to viral-induced

injury. Astrocytes may play a minor role in the CNS as antigen-presenting cells and seem to be capable of some phagocytic activities.

The factors that may activate glial cells in the inflammatory response have begun to be identified, but how the whole process is orchestrated in an orderly fashion is still to be clarified. A bewildering array of cytokines, monokines, growth factors, and other mediators can induce glial cell proliferation, including glial cell-stimulating factor,²⁸ interleukin-1,^{29,30} microglial mitogens,³¹ and others.³² These are derived from a number of sources, including intrinsic glial cells themselves and hematogenous cells.

Many viral agents infect neurons, either exclusively or as part of a wider tropism for CNS elements. The response to infection of the soma may vary from swelling and chromatolysis to shrinkage and increased basophilia. Satellite oligodendrocytes (and perhaps other satellite glial cells) react to the degenerate perikaryon by proliferation, forming a collar of cells one or two cells deep about the degenerating cell body. This process is known as **neuronal satellitosis**. Progressive demise of the neuron is marked by its piecemeal division and phagocytosis, eventually leaving a dense nodule of glial cells and fragments of the former neuron (**neuronophagia**) (Fig. 1-34).

DEMYELINATION

A select few inflammatory neurological diseases are marked by primary demyelination. This is relatively rare; for example, demyelination of any consequence is not a feature of bacterial, mycotic, or protozoan encephalomye-

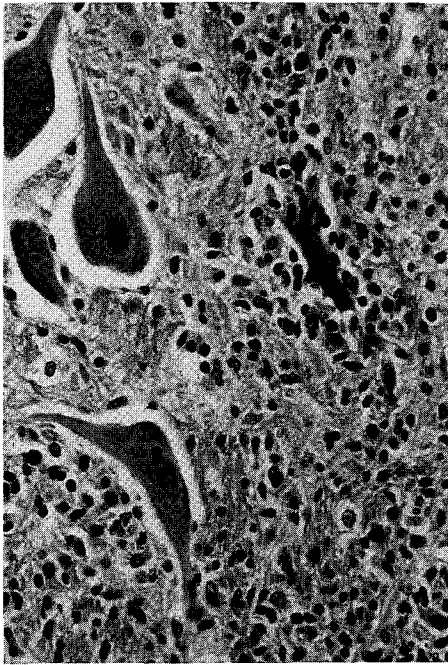


Fig. 1-34. Neuronophagia: The degenerate neuron, shrunken and dark, has attracted many scavenger cells. Compare with healthy neurons at left. (H&E, $\times 350$.)

litides, and it is associated with only a few viral agents.^{33,34} Where observed, it is an important hallmark of the disease. The inflammatory neuraxial disorders in domestic animals in which demyelination is found are canine distemper, visna, and caprine arthritis encephalitis syndrome. In none does CNS demyelination occur as the predominant central feature of the disorder as in human **multiple sclerosis**.

The demyelinating process may be triggered by the infectious agent alone (as perhaps in murine coronavirus encephalitis) or by an immunopathological reaction triggered by the agent (visna, caprine arthritis encephalitis syndrome, murine Theiler's virus encephalomyelitis), or an agent may be only suspected (multiple sclerosis). Most concepts of the mechanisms of virus-induced central demyelination invoke immunopathological mechanisms. This position is taken because evidence is rare that primary demyelination results from infection of oligodendrocytes, leading to cell disruption or lysis. There is such evidence for oligodendrocyte infection in murine JHM coronavirus encephalitis,³⁵ although its importance has been challenged³⁶; in murine Semliki Forest infection³⁷; and in human progressive multifocal leukoencephalopathy.³⁸ In these three and other diseases, oligodendrocytes are not the only cells susceptible to viral infection. In some diseases such as canine distemper encephalomyelitis, evidence of oligodendrocyte infection has been demonstrated, but its contribution to the demyelinated state is unclear.^{39,40}

Proposed mechanisms of immune-mediated demyelination include the following:

1. The infectious agent produces a noncytolytic infection of the oligodendrocyte, but an immune response to viral determinants expressed at the cell surface leads to cell death.
2. There are shared antigenic determinants between the virus and the oligodendrocyte–myelin sheath complex. An immune response generated by the agent also leads to an attack on host tissue. Such would not require that the agent be present in the CNS. The occurrence of sequence homology between CNS proteins and a number of viruses has been shown,^{41,42} but the significance of the observation for neurological disease remains to be established. Molecular mimicry with reactivity to a number of normal tissues was found with several antiviral monoclonal antibodies and may be common.⁴³
3. Some viruses incorporate cellular membrane or cytoskeletal elements such as tubulin and actin into the virion during replication or assembly,⁴⁴ hence possibly triggering an antiself response.

How cytotoxic CD8-positive T cells would effect demyelination is unclear as oligodendrocytes and myelin express little or no MHC class I antigen. Presumably collaboration occurs between T lymphocytes and other cells such as macrophages or astrocytes and with immunoglobulins.⁴⁵ This could result in the release of oligodendrocytotoxic or myelinotoxic factors such as tumor necrosis factor, nitric oxide, lymphotoxin, perforin, complement, and acidic and neutral proteases.⁴⁶⁻⁵⁵ Macrophages internalize and digest the myelin debris (Fig. 1-35).

In demyelinating diseases, the selective loss of the ensheathing myelin coat, although leaving the underlying axon naked but intact, requires a very specific attack upon the myelin sheath or the cell that makes it. The theory of **bystander demyelination**⁵⁶ proposes that a cell-mediated immune response to any antigen in white matter, by generating the release of proteases, lymphokines, and the like, could nonspecifically induce myelin injury. However, common experience shows that demyelination does not occur to any significant degree in the vast majority of central inflammatory diseases. It has been shown that a form of antibody-dependent bystander demyelination may be operative in canine distemper encephalomyelitis. This involves a specific humoral response to distemper virus and subsequent binding of antibody to macrophages, triggering the release of reactive oxygen species to which oligodendrocytes are very sensitive.⁵⁷

In humans, both central and peripheral demyelinating or necrotizing white matter disorders occur as postinfectious phenomena following respiratory tract infections or after vaccinations, and they are thought to have an allergic basis.⁵⁸ Comparable conditions are not recognized in animals, with perhaps the exception of canine polyradiculoneuritis, which is somehow triggered by a raccoon bite. Demyelination is a central theme in experimental autoimmune encephalo-



Fig. 1-35. Electron micrographic demonstration of myelin phagocytosis. This macrophage has internalized large myelin fragments (*M*) and tiny myelin figures (*F*), the latter via surface-coated pits (*arrows*). ($\times 11,670$.)

myelitis (EAE) and experimental autoimmune neuritis (EAN). These disorders are induced by the inoculation of laboratory animals with CNS or PNS myelin antigens in adjuvants or by the passive transfer of T cells sensitized to these immunogens. In EAE and EAN, an infectious agent is not involved.

INFECTIOUS AGENTS AND CNS INFLAMMATION

Many inflammatory diseases of the CNS are caused directly or indirectly by infectious agents, of which there are diverse types including viruses, bacteria, fungi, protozoa, rickettsia, and amebae. Among the domestic animals, there appear to be no known instances of primary neurological disease and encephalomyelitis caused by *mycoplasma* infections, although some mycoplasma infections produce meningitis as part of a polyserositis. In **turkeys**, meningeal vasculitis (Fig. 1-36), nonsuppurative meningoencephalitis, and focal necrosis of various areas of the brain have been associated with *Mycoplasma synoviae* and *M. gallisepticum* infections.^{59,60} Clinical signs in affected turkeys have included ataxia, torticollis, and recumbency. Fibrinoid vasculitis may also be found in arterioles in visceral organs. This group of organisms may play an unrecognized role in mammalian neuropathology. For a review of the neurological disorders of poultry, which are discussed only briefly in this book, see Helmboldt⁶¹ and Pattison.⁶²

The most comprehensively studied neuropathogenic in-

fectious agents of humans and other animals are the **viruses**.⁶³ Many encephalomyelitides occur as part of a more generalized viral infection, but involvement of the CNS is commonly the cause of morbidity and mortality. The patterns of viral disease run the gamut from acute infections, which may be rapidly lethal (rabies, pseudorabies) to persistent, tolerated infections such as Border disease, which are acquired in utero. Persistent infection with the bovine virus diarrhea agent in cattle (which is closely related to the Border disease agent) produces extensive neuronal infection in the neocortex and hippocampus,⁶⁴ some detectable degenerative and inflammatory changes,⁶⁵ but no evidence of neurological disturbance. Hence it is important to distinguish between infection and disease. Intermediate perhaps between acute disease and a state of tolerance is that in which there is no obvious morphological change in the infected cell population, but normal synthetic activities of the tissue are lost: Oldstone's so-called loss of luxury function. In latent infections, the agent persists without replicating but can be reactivated, typified by the herpesviruses in craniospinal ganglia. Some viruses act as direct pathogens, whereas others instigate disease indirectly by triggering immune-mediated tissue injury. If the infecting virus is non-cytopathic, a strong cytotoxic immune response is only to the host's detriment.

Neuropathogenic viruses include conventional DNA and RNA viruses, the somewhat more atypical retroviruses that incorporate into the host's genome, and (to use the term virus loosely) the unclassified scrapie group. The retrovirus family contains three subfamilies: oncoviruses, lentiviruses, and spumaviruses. Members of all three subfamilies can invade the CNS,⁶⁶ but only oncoviruses and lentiviruses are associated with spontaneously occurring neurological disease. Sporadically or frequently, these agents are neuropathogenic in a wide range of animals and in humans.

1. Sheep: visna
2. Goat: caprine arthritis encephalitis virus
3. Cat: feline immunodeficiency virus
4. Human: human immunodeficiency virus, human T cell lymphotropic virus type 1
5. Mouse: murine leukemia virus
6. Horse: equine infectious anemia virus

Bovine immunodeficiency virus is mainly associated with lymphocytosis and lymphoid hyperplasia⁶⁷ and is not yet a proven CNS pathogen. Involvement of a canine retrovirus is conspicuously lacking from the list, but it will be surprising if a role for a canine retrovirus in neurological disease is not established. In this group of viruses, infection of monocytes and a tropism for macrophages are crucial to neurovirulence.⁶⁸

For some diseases, there is immunological evidence incriminating a viral cause (such as the sheep-associated form of malignant catarrhal fever), and others (multiple sclerosis) are thought to be acquired infections largely on the basis of epidemiological data. Some viruses are important pathogens

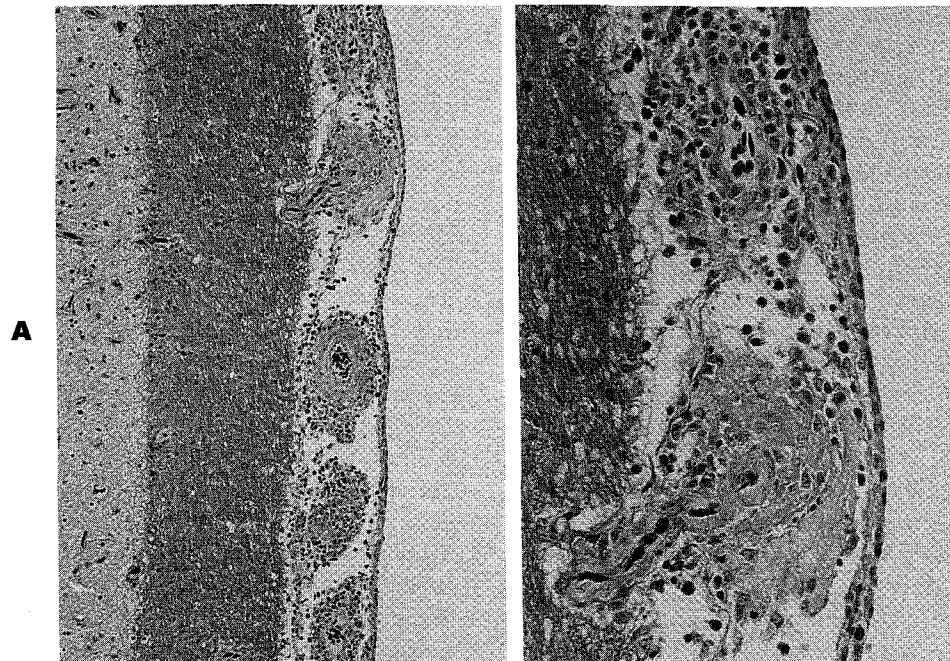


Fig. 1-36. *Mycoplasma vasculitis*, optic lobe, turkey. **A**, Several affected meningeal arterioles. (H&E, $\times 140$.) **B**, Enlargement showing the vasculitis and fibrinoid necrosis. (H&E, $\times 350$.)

for the developing nervous system but express their effects in quite different organ systems postnatally (feline parvovirus, ovine bluetongue virus).

The pathogenic effects of viral infection vary remarkably. Fetal infection may result in death, aberrations in CNS development, or a fairly conventional nonsuppurative encephalomyelitis, depending on gestational stage at the time of infection. In the midperiod, infections of germinal neuroepithelial cells in the fetus are lytic, resulting in segmental failure of brain development. This may be manifest in the cerebrum as hydranencephaly or in the cerebellum as hypoplasia. Most CNS infections are acquired after birth. Studies of the interplay between viral agents and their hosts show that both host and agent factors bear on the outcome of the interaction. In studies of viral encephalomyelitis, significant effects are often associated with the genetic background of host, the age of the host at the time of infection, the immune status of the host, and the strain of the virus. In general, CNS infections in neonates are much more virulent than in juvenile or mature animals. Infection of neonates with neurotropic viruses commonly induces necrotizing changes with prominent neuronal (gray matter) damage and high mortality. This contrasts with an increased tendency for white matter injury thereafter, usually associated with more subacute to chronic disease. Such can be shown for Theiler's virus and JHM coronavirus encephalomyelitis in mice,^{69,70} and for canine distemper encephalomyelitis in dogs.⁷¹ Most natural viral infections of the CNS are mixed (gray and white matter), with often one pattern or the other predom-

inating. The most highly neurotropic viruses produce the purest pattern of gray matter injury, whereas enhanced demyelinating disease can be selected with viral variants, such as temperature-sensitive or other mutants.^{72,73}

Cell surface receptors are recognized as very important determinants of susceptibility to infection.⁷⁴ Some viruses infect both neuroectodermal and mesenchymal components of the CNS; some infect only mesenchymal cells (often blood vessels), whereas many infect neurons and glial cells; some infections are limited to a single neuroectodermal cell type such as neurons or ependyma, in a limited topographic distribution. In humans, HIV infection seems to be targeted to microglial cells that have the CD4 receptor⁷⁵ as well as to T-helper cells in lymphoid tissues. In murine encephalitis caused by reovirus type 3, a selective tropism for neurons is found both *in vivo* and *in vitro*.⁷⁶ Some CNS diseases are limited to very precise periods of life, perhaps because the expression of viral receptors on target cells is transient. One such example is avian encephalomyelitis, a disease of young chicks, where susceptibility to infection of spinal cord somatic motor neurons in the neonatal period seems to be critical. In experimental Japanese encephalitis virus (JEV) infection in rats, infection of neurons was closely associated with neuronal maturity.⁷⁷ Infection was widespread with 100% mortality at 1 day of age compared with minimal infection and only 8% mortality at 14 days. Fetal neurons transplanted into neonatal mice were susceptible to JEV infection, whereas the host neurons showed the age-related resistance. Indeed, the limitation of some virus infections

to a group of cells is a measure of the degree of specialization within the CNS. Although we think of the CNS as containing neurons and glial cells, this classification should be viewed as rank oversimplification. In reality, these are structurally and functionally diverse populations, and probably for the glia there are subpopulations within a lineage. As Johnson has commented,⁷⁴ the effects of viral infections of the neuraxis are varied because distinct cell populations have different susceptibilities to different viruses, and viral infections can have varied effects on host cells.

The microscopic hallmarks of CNS inflammation have been previously discussed. In putative viral infections of the CNS, the pathologist searches for evidence of inflammatory changes and for pathological alterations in neurons and glia, such as chromatolysis or inclusion body formation. Viral inclusions are amphophilic or eosinophilic and may be intracytoplasmic, intranuclear, or both. Pseudoviral inclusions can trap the unwary; they are reviewed in the discussion of rabies. The topography of the brain lesions is helpful in some viral diseases (postvaccinal form of canine distemper) and less so in others. Immunocytochemical studies often show that infection of permissive cells in the tissue is much more pervasive than either cytopathic changes or inflammatory reactions would suggest. Indeed, an overwhelming viral encephalomyelitis may be fatal before any morphological changes have had time to develop. In CNS viral infections that are successfully aborted, the pathological landmarks in recovering animals are the presence of very sporadic, small, perivascular cuffs of mononuclear cells, occasional foci of gliosis throughout the tissue, and a variable pleocytosis of the CSF.^{78,79} Viral clearance from the CNS seems to lag behind clearance in other organs and is effected with minimal cell lysis.⁸⁰

NEUROINVASIVENESS AND NEUROVIRULENCE

Neuropathogenicity is complex. First, the agent in question must persist in nature, which can be effected by transmission from host to host at short intervals, resistance in the environment, or chronic persistent infection in the host.⁸¹ Second, virus must be successfully transmitted to naive hosts, which may occur in utero or postnatally by one of several routes. Following infection, there is commonly a phase of replication in peripheral tissues (lymphoid organs, vascular endothelia, skeletal muscle, or other tissue). The microbe must then gain access to the nervous system (which is mostly by the vascular route) and find cells there that are permissive. Many viruses are less or more immunosuppressive, which allows much of this chain of events to unfold before specific humoral and cellular immune responses can be mounted. Many persistent infections involve the CNS (visna in sheep, Borna in horses, subacute sclerosing panencephalitis in humans), and the agents in question have devised a variety of maneuvers to frustrate the host, including limited antigenic expression in infected cells, the

existence of the agent as integrated provirus, antigenic drift, latent infections, and defective infection with spread limited to cell-to-cell transfer. Viruses may survive happily within neurons, as these cells fail to express MHC class I antigens and so are not targets for cytotoxic T cells.⁸² In some viral infections, the mechanism of viral persistence in the CNS is not understood. Some agents seem to persist latently in the CNS but are reactivated if the host becomes immunosuppressed, such as *Toxoplasma gondii* and papovavirus (JC) infection in humans.

Studies of persistent viral infections have shown that, within the infected host, segregation of virus can occur with emergence of different strains in different organs. In chronic murine lymphocytic choriomeningitis virus infection, isolates from the CNS of adult mice induced acute infection in recipients, whereas splenic isolates produced chronic infections.⁸³ Segregation has been shown with lentiviruses including equine infectious anemia virus⁸⁴ and simian immunodeficiency virus.⁶⁸

Pathogenicity for the CNS can be viewed as a combination of (1) **neuroinvasiveness**, the ability to invade the host, replicate, and reach the CNS; and (2) **neurovirulence**, the capacity to produce a deleterious effect in the target organ.⁸⁵ These two properties are ascribed to different segments of the viral genome. They can be studied separately, for example, by direct inoculation of the agent into the brain, which largely circumvents the neuroinvasiveness factors.

Central nervous system invasion is thought to occur by means of the hematogenous route with all but the most highly neurotropic viruses. During viremia, virus particles may be free in the plasma or the viremia may be cell-associated, with virions within cells such as monocytes, lymphocytes, neutrophils, or even platelets. A number of neurotropic viruses such as visna, caprine arthritis encephalitis virus, canine distemper, measles and HIV infect leukocytes. The CNS invasion may follow endothelial cell infection or occur by the "taxi" method, whereby migrating leukocytes carry the agent into the neuroparenchyma. Infection of the choroid plexus offers ready access to plexus epithelial cells and their surface macrophage population (Kolmer cells), which can introduce infection into the CSF pathways. Vascular dissemination will also deliver virus to the leptomeningeal fibrocytes and to vascular pericytes.

Rabies virus and several herpesviruses express their highly developed neurotropism by reaching the CNS via motor and sensory nerves.⁸⁶ In domestic animals, this occurs in rabies and in Aujeszky's disease. Whether viral movement occurs within the axon, from cell to cell in the nerve sheath, or in the interstitial spaces has been argued. Experimental data seem to favor an intraaxonal route, with axonal and transsynaptic spread within the neuraxis.^{87,88} A neural pathway into the brain may be operative for viral infections that spread to the olfactory mucosa, given its proximity to the olfactory bulb.⁸⁹ Dendrites of bipolar ol-

factory neurons are within the olfactory mucosa, terminating as small vesicles at the epithelial surface. This pathway may be important in some herpetic and arthropod-borne viral infections. How the neuropathogenic enteric viruses (such as the picornaviruses, reoviruses, and coronaviruses) reach the CNS remains controversial, as there is evidence for both hematogenous and neural routes.⁹⁰ In murine reovirus infection, it seems that reovirus type 1 takes a hematogenous path to the CNS (although some neuronal infection can be found),⁹¹ whereas type 3 employs an axonal route, using microtubule-associated fast axonal transport. Passage of type 3 reovirus through the Peyer's patches into the autonomic plexus and the vagus nerve has been demonstrated.⁹² Segments of the reovirus genome have been identified that determine which route will be taken to reach the CNS.⁹³ Passage of virus from the intestine to autonomic nerves has also been suggested for vomiting and wasting disease in pigs (coronavirus) and for Aujeszky's disease in dogs (herpesvirus) following the ingestion of infected swine tissues.

Contemporary techniques in biology permit the investigator to explore the pathogenesis of disease at the molecular level. A number of laboratory animal models of viral encephalomyelitis have been subject to such close scrutiny. Studies in mice have the advantages of allowing considerable manipulation of the host (genetic background, production of transgenic animals), the availability of antisera or monoclonal antibodies to T cells and their subsets, B cells, and macrophages, and the fact that recombinant constructs of the viral agent can be prepared and tested. Such studies address areas ranging from viral entry into the CNS to determinants of neurovirulence. For example, the ability of herpes simplex virus to gain access to the CNS in mice (neuroinvasiveness) can be ascribed to the gene that codes for glycoprotein D.⁹⁴ After limb or footpad inoculation in mice, reovirus types 1 and 3 spread to the spinal cord by the bloodstream or peripheral nerves, respectively. The protein determining which pattern of spread will be operative seems to be the viral hemagglutinin.⁹³ The ability of Theil-

er's virus to establish persistent infection and demyelination in mice is host-dependent and strain-dependent. Studies with viral strains that produce acute gray matter or chronic demyelinating white matter disease and with chimeric viruses permitted these determinants to be mapped along the genome.⁹⁵⁻⁹⁷ Remarkably, a mutation in a single amino acid in the RNA of the VP1 (a capsid protein) coding area renders pathogenic virus relatively avirulent.⁹⁸ Viral envelope glycoproteins are important in governing the outcome of some neurotropic infections, probably because they are ligands for binding to receptors on neural cells such as neurons, thus mediating cell tropism. They also have other functions such as fusion and hemagglutination.⁹⁹ Sindbis virus (alphavirus) neurovirulence for weanling mice is influenced by the E1 and E2 glycoproteins.^{100,101}

Just as determinants that are important for pathogenicity and immunity have been defined in the viral genome, the specific elements of the host's immune armamentarium have been investigated. Nude mice can be protected against the spread of influenza virus from lungs to brain by the adoptive transfer of cytotoxic T cells.¹⁰² In mice and rats, clearance of coronavirus from the CNS involves both CD4 and CD8 T cells,¹⁰³⁻¹⁰⁵ and the importance of CD8 cells in protection against herpesvirus and Theiler's picornavirus infection of the nervous system in mice has been demonstrated.^{106,107} Curiously, measles virus encephalitis in rats could be cleared by CD4 T cells alone,¹⁰⁸ although an earlier study demonstrated a role for CD8 cells.¹⁰⁹ Concurrent with cell-mediated effector mechanisms, a strong humoral immune response¹¹⁰ is important to neutralize free extracellular virus particles. Antiviral antibody may be particularly important in clearing neuronal infections,¹¹¹ as these cells do not express MHC class I molecules and so are not susceptible to virus-specific CD8 cytotoxic T lymphocytes. Antibody can enter cells by endocytosis and may neutralize virus within cells.¹¹² Little is known of the role of natural killer cells in neurological disorders.^{78,113}

References are on p. 63.

Ancillary procedures in neurological disease

Many ancillary procedures may be employed in evaluating the patient with known or suspected central or peripheral nervous system disease.¹

1. Imaging procedures such as radiography, computed axial tomography, nuclear magnetic resonance studies, myelography, and scintigraphy
2. Electrodiagnostic testing procedures such as electromyography and measurements of nerve conduction ve-

locity, electroretinography, brain stem auditory evoked responses, and electroencephalography

3. Muscle biopsy, fascicular nerve biopsy, and, with increasing frequency, brain (particularly tumor) biopsy
4. Serum biochemical and hormonal analysis and cerebrospinal fluid analysis

Analysis of CSF provides important data for the clinician, and the neuropathologist equally can be guided by the results

of this examination. Spinal fluid is routinely sampled in small, large, and exotic animal species, and several papers define the range of "normal" values for a number of parameters and the changes found in the spectrum of neurological diseases. Comprehensive reports are available for the **dog** and **cat**²⁻¹⁴ and the **horse**,¹⁵⁻¹⁹ but there are fewer published studies for **ruminants** and **other species**.^{20,21} In attempting to provide reference values, many papers have described the results of analyses of normal animals. For any given species, there is some variation within these reports. Many factors potentially contribute to this dispersion: whether the sample was drawn from the atlanto-occipital or lumbar sites, if there was any contamination with blood, how rapidly after collection and by what technique the sample was analyzed, and probably other factors. In some species, normal lumbar CSF contains more protein than does an atlanto-occipital sample³ and a spinal cord or a radicular lesion is more likely to yield an abnormal lumbar sample or a higher protein level than is a cerebellomedullary sample.^{9,20} In practice, each laboratory must establish its own parameters—which hopefully will be comparable to, if not identical with, those of other institutions—and work from that basis. As a rule of thumb, we allow up to five nucleated cells per cubic millimeter in all domestic animals; up to 25 mg of protein per deciliter in dogs and cats, 45 mg protein in ruminants, and 70 mg in horses. It must also be remembered that elevated protein levels in CSF occur with spinal root diseases.

In a routine analysis, the clinical pathology laboratory reports on the physical appearance of the CSF sample (e.g., clear, xanthochromic, or turbid) and provides the total and differential white blood cell count and the total protein level of the sample. Lymphocytes, monocytes, and plasma cells are anticipated in the specimen with most viral diseases, and mixtures of polymorphonuclear cells, macrophages, and lymphocytes in bacterial and fungal diseases and immune-complex disorders.^{8,22} Many further parameters can be evaluated, including CSF pressure (opening and closing), albumin concentration, proportion of α -, β -, and γ -globulins, complement level (usually C3), glucose, electrolytes, and enzymes (often creatine kinase^{18,23} and sometimes others). Sporadically, infectious agents are found within the sample, either free (classically in cryptococcosis) or identified within phagocytes (neutrophils, monocytes) in stained preparations (bacteria, fungi); in such cases, CSF cultures are worthwhile. In general, viral encephalitides must be examined very early in the clinical course if virus isolation from CSF is to be successful, but PCR and in situ hybridization may favorably alter such studies. Analysis of CSF for virus-neutralizing antibodies may be informative if it can be shown

that the titer does not simply reflect a "spillover" of serum immunoglobulins into the CNS. This can be addressed by comparing the levels of a second antibody in serum and CSF in the patient (e.g., in dogs parvovirus, adenovirus, or parainfluenza virus antibody would suffice).

The CSF is an ultrafiltrate of plasma to which are added substances (electrolytes, hormones) actively secreted into it by the ventricular lining cells. Normal protein concentration and composition depend on the integrity of the blood-brain barrier (BBB). The CSF contains protein (albumin and α -, β -, and γ -globulins) at approximately 1/200 the concentration of that found in blood. Elevated levels of albumin within the CSF indicate BBB disruption with leakage from the peripheral circulation. The hallmark of canine granulomatous meningoencephalitis is mixed mononuclear cell infiltration around CNS blood vessels. This must significantly disrupt the BBB, for CSF protein levels may be very high²⁴ with an appreciable albumin component.¹¹ In spinal cord injury from acute disk extrusion or with brain tumors, protein levels may be elevated (albumin, α - and β -globulins), but the γ -globulin levels are relatively normal. Increased γ -globulins may result from intrathecal synthesis, may be derived from the blood, or may come from both sources. In chronic canine distemper encephalomyelitis, the BBB may be intact, but CSF protein levels are elevated because of immunoglobulin production by plasma cells within the brain, spinal cord, and leptomeninges.^{25,26}

Studies of a persistent intrathecal humoral immune response have been pursued most extensively in multiple sclerosis in humans. Formulas have been derived to provide the required **immunoglobulin index** or **quotient**.²⁷ Similar calculations have been devised for dogs and cats^{5,12,14,25,26,28} and for horses.²⁹ The IgG index can help to substantiate or deny the presence of inflammatory CNS lesions.²⁸

In humans, many primary or secondary CNS tumors are identified because neoplastic cells seed into the CSF. In animals, there are exceptionally few reports in which this observation has been made. This difference (from humans) may reflect biological differences in tumor growth and behavior or the fact that the clinical course for human patients with neuraxial tumors is usually much longer than for animals. However, a significant element is probably the need for veterinary clinical pathologists (and their technicians) to be aware that CSF samples may harbor neoplastic cells. In dogs and cats, oligodendroglioma, ependymoma, lymphoma, and metastatic carcinoma have been identified from CSF examination.^{5-8,30,31} Elevation of CSF pressure, protein level, and leukocyte count may be found with brain tumors.^{31,32}

References are on p. 65.

Neuropathology of aging

Introduction
 Neuronal and glial populations
 White matter
 Inclusions within cells
 Leptomeninges, choroid plexus, and blood vessels
 Alzheimer's disease and pathological comparisons in animals

INTRODUCTION

The expected lifespan of Western man is approaching 75 to 80 years. Over the course of this period, manifestations of degenerative changes appear in most organ systems: Pigment is lost from the hair, visual acuity falls, changes in the connective tissue matrix of the skin become evident, athletic abilities wane, articular cartilages of the diarthrodial joints become fibrillated and frayed, in women menstrual cycling ceases, and sometimes higher cerebral functions (cognition, memory) decline. Thus, with advancing age, signs of deterioration can be anticipated in many organ systems. In some circumstances, it is not difficult to separate a pathological process from the physiological effects of aging; for example, a 40-year-old patient with Alzheimer's disease who cannot identify family members, cannot tell the time, and cannot remember to eat meals (or when the last meal was taken) clearly has a devastating neurological illness. In contrast, we are less alarmed by the octogenarian who has the occasional bout of forgetfulness, becomes confused at times, misnames people, and so on. Somewhere between these two extremes, the "normal" onward march of organ decline encounters a number of degenerative diseases, but the point of transition from one to the other is often unclear and of necessity has sometimes been decreed arbitrarily.

Many of the degenerative changes in tissues just listed are encountered in veterinary medicine in the geriatric population of companion animals (dog, cat, and horse). With respect to the CNS, a statement can be made that applies equally to all diseases of humans and animals: Some disorders are highly comparable, some share some points of similarity, and others are limited to humans or to individual animal species. Thus neuronal lipofuscinosis in the aged human being and the elderly dog are probably analogous conditions, whereas the full neuropathological spectrum of Alzheimer's disease is not encountered spontaneously in any of the domestic animals.

In general, the effects of the aging process on the CNS have received scant attention in veterinary medicine. For example, geriatric cerebral atrophy is well recognized in humans, but in routine animal pathology it is not normal

practice to weigh the brain at necropsy (or even always to remove the brain from the cranium). Accordingly, we have no universal data from which to evaluate whether a comparable state of age-related regression of the brain occurs in domestic animals. An impression that we have gained over many years is that, if cerebral atrophy occurs in old dogs and cats, it is apparently mild. Several authors comment that the brains of old dogs are mildly hydrocephalic. Only in general terms can we compare the brain of an aged human (say, 85 years) with an aged dog or cat (say, 15 to 20 years).

The impetus for many studies of the aging animal brain has been an attempt to identify pathological alterations comparable to those encountered in humans; they include the search for cerebrovascular amyloidosis and senile plaques in the brain of aged domestic animals and primates. The majority of the conditions we shall describe in domestic animals are incidental changes in the brain and spinal cord. Veterinary pathologists should learn to recognize these lesions and be cautious before ascribing clinical significance to them.

NEURONAL AND GLIAL POPULATIONS

In animals, there are notably few studies of changes in CNS cell populations with aging. Furthermore, most researchers have turned their attention to laboratory rodents rather than to domestic animals in these investigations. Some studies employ the cat, but this animal is used widely in neurological investigations, particularly neurophysiology. A common theme emerging from these studies is that as animals age, degenerative changes and/or depletion are found in some neuronal populations. In contrast, neuroglia may be reduced in number, remain constant, or even increase in the aged. That the effects of aging are selective is well illustrated in Sturrock's studies of the **mouse** cerebellar cortex between 6 and 31 months of age¹; whereas Purkinje, stellate, and basket cells all were lost, granule cell density remained constant. In the trigeminal complex of the mouse, neurons of the mesencephalic nucleus are lost before those of the motor nucleus.² In a study of spinal motor neurons in aged **rats** (27 months), significant loss was found in the lumbar, but not the cervical, enlargements.³ Neurophysiological studies of the caudate nucleus in the **cat** have shown reduced excitability, which has been correlated with diminished synaptic density in animals older than 3 years⁴ and a loss of dendritic spiny processes after 6 years. In studies of the brains of aged **dogs** with congophilic angiopathy and senile (neuritic) plaques, a loss of neurons from the neocortex in laminae III and V⁵ or from unspecified areas⁶ have been reported.

Many owners of aged dogs note an apparent deafness in their pets; it is sometimes difficult to establish whether they truly cannot hear or simply choose to ignore being called, and indeed their aged owners often behave similarly. However, quantification of spiral ganglion neurons revealed an age-associated reduction, the most severe being in 15- to 17-year-old dogs, which appeared to be deaf and lacked brain stem auditory evoked responses.⁷

A study of gliosis in aged nude mice (18 to 29 months) revealed a marked increase in GFAP-reactive fibrillary astrocytes.⁸ This was most pronounced in cerebral hemispheric white matter, corpus callosum, hippocampus, and middle cerebellar peduncle. A similar study in the dog⁹ showed a widespread, age-related astrogliosis involving gray and white matter, including the corona radiata, corpus callosum, internal capsule, brain stem, and cerebellar nuclei. In contrast, quantification of neuroglial cells (differentiation of glial cell types was not attempted) in the facial, retrofacial, and trigeminal nuclei of mice revealed only mildly fluctuating numbers between 6 and 31 months of age,¹⁰ sometimes with increases and other times with a reduction in glial numbers. Neuronal satellite glial cells seem to be more prominent in aged animals, giving the impression of satellitosis.¹¹

WHITE MATTER

Idiopathic degeneration of the spinal cord funicular white matter occurs in mature and aged German Shepherd dogs and other large dog breeds. This disorder has been variously named, including canine degenerative myelopathy and German Shepherd myelopathy, and is discussed with the degenerative diseases. A somewhat similar myelopathy is common in a variety of strains of aged laboratory rats and is also considered with the canine disease. Sometimes these disorders in the dog and rat have been termed radiculomyelopathy to encompass the ballooning degeneration of Schwann cell myelin sheaths in the dorsal and ventral spinal roots. We have observed this degeneration of peripheral myelin of the intradural lumbar roots in a large number of domestic and exotic animal species as an incidental finding at necropsy, unassociated with leukomyelopathy.¹² It is discussed further in Chapter 7.

There is a degenerative change in the white matter of many aged **dogs** (typically over 12 years old) that we and other investigators (McGrath, personal communication, 1985)¹³ have noted. The degeneration affects densely myelinated tracts such as the corpus callosum, corona radiata, and hippocampal alveus and appears to be an incidental observation at necropsy. The alteration is a pallor and fine vacuolation of the myelinated fibers, the appearance of isomorphic gliosis, and the accumulation of perivascular macrophages containing a pale yellow pigmentary material (Fig. 1-37). The gliosis takes the form of elongation and hypercellularity of the chains of interfascicular glia and

is quite distinct from that associated with inflammatory disorders. Pigment in the perivascular histiocytes is probably derived from myelin degeneration and will stain with luxol fast blue.¹⁴ It has been designated variously as lipid¹⁵ and lipofuscin,¹⁶ but Jolly suggests the term ceroid, to be limited to lipopigments formed from lipid degeneration and/or peroxidation.¹⁴ Ubiquitin- and galactocerebroside-immunoreactive granules and globules have been demonstrated in these degenerate white matter tracts.¹³ In old **rats**, particularly older than 24 months of age, idiopathic vacuolar change in brain white matter is common.¹⁷ This change is found in the thalamus, midbrain, pons, and cerebellum and, when severe, in cerebral white matter.

Focal axonal swellings—**spheroids**—are a nonspecific response to many diverse insults, including trauma, hypoxia, intoxications, nutritional deficiencies, and storage disorders. Axonal spheroids are also encountered in the CNS (Fig. 1-38) and the autonomic ganglia with increasing frequency with progressive age.¹⁸ Spheroids in low numbers may be found at all ages and at all levels of the neuraxis but are generally more common in the aged, in the gray matter more than the white matter, and particularly in the medulla (nucleus gracilis and also the nucleus cuneatus) and sacral spinal segments. In the horse, the demonstration of axonal spheroids in the lateral cuneate nucleus is taken as one diagnostic feature of equine degenerative myeloencephalopathy, but Abbott has shown their abundance in this nucleus in foals with nonneurological diseases in the first year of life.

Spheroids are focal distensions of the axon with organelles that normally are in transit toward the axon termination or returning to the soma of the neuron. The swellings vary from circular to fusiform in shape and measure up to 200 microns.¹⁹ They are eosinophilic and vary from having a homogeneous appearance to granular, vesicular, or vacuolated. Sometimes the spheroid contains several vacuoles (giving a multiloculated appearance), and the vacuoles appear to expand, eventually obliterating all visible axoplasm. Accordingly, at low power of an affected nucleus, the observation of a mixture of eosinophilic swellings and vacuoles (apparently in the neuropil) is common. Spheroids are argyrophilic²⁰ and in a fortuitous silver-stained section it is possible to visualize a segment of the axon and its focal swelling. Ultrastructurally^{19,21} they may be found in myelinated or unmyelinated fibers, typically at or near the axon terminations of primary sensory neurons.²² If a myelin sheath is present, it typically is attenuated by the swollen axon. A variety of organelles may constitute the swelling; some spheroids consist largely of maloriented neurofilaments and microtubules, presumably in anterograde transport. Some contain abundant profiles of smooth endoplasmic reticulum or other tubulovesicular bodies. A common type contains amorphous dense bodies, mitochondria (which may have matrical densities), and other degenerate

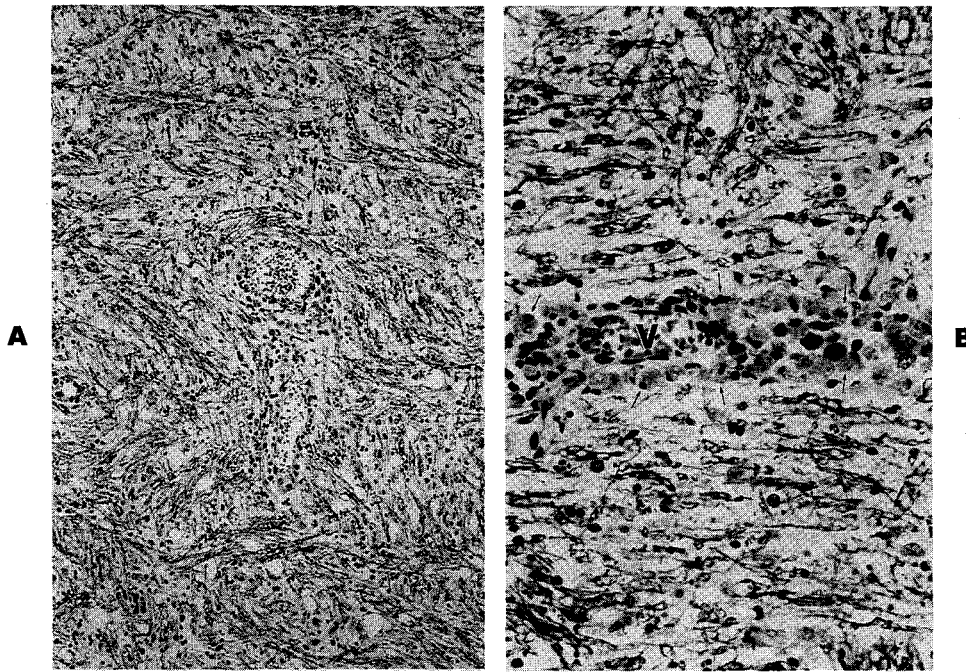


Fig. 1-37. Aging change in cerebral white matter, dog. **A**, Diffuse fine myelin vacuolation and gliosis. (Luxol fast blue, cresyl echt violet, $\times 140$.) **B**, Vacuolar disruption of myelin sheaths. Perivascular collection of macrophages with granular lipopigment (*arrows*). V, vessel. (LFBCEV, $\times 350$.)

organelles, which are probably returning to the cell body for recycling.

Quantitative studies in laboratory animals have shown progressive degeneration and atrophy of fibers in the fasciculus gracilis as an effect of aging.²² Our impression gained over many years from the study of spinal cord diseases in domestic animals is that occasional degenerate fibers are seen incidentally in mature and aged animals. They are seen as single, isolated chains of myelin ellipsoids in an otherwise normal funiculus. This survey is facilitated by sectioning the spinal cord longitudinally, as well as taking the conventional transverse section.

INCLUSIONS WITHIN CELLS

In a variety of domestic and nondomestic animals, eosinophilic intracytoplasmic inclusion bodies, which may be mistaken for the rhabdovirus inclusions (Negri bodies) of rabies encephalomyelitis, occur normally or nonspecifically within neurons in the brain. The neuronal populations that harbor these inclusions vary with the species in question. These pseudo-Negri bodies are reviewed in the section on rabies. In two animals, the appearance of similar inclusions seems to be associated with progressive aging: These are the eosinophilic intracytoplasmic bodies in thalamic neurons

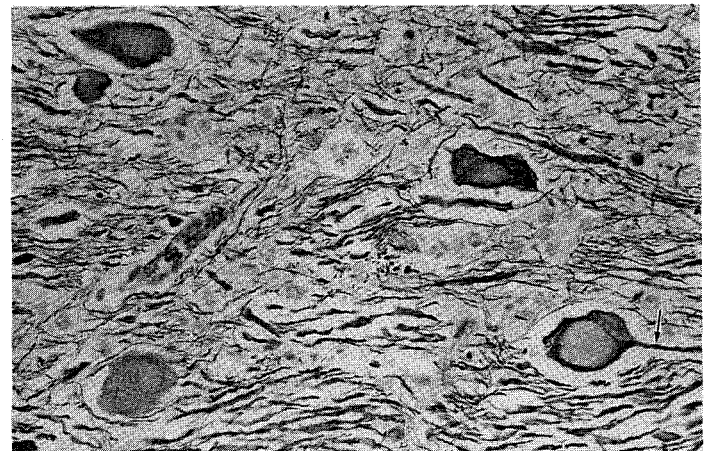


Fig. 1-38. Spheroids shown by silver impregnation, cat. Note continuity with a normal axon at arrow. (Holmes, $\times 350$.)

in mice²³ and those in the large reticular neurons of the brain stem of woodchucks.²⁴

A novel intracytoplasmic inclusion occurring in neuronal perikarya of old dogs has been recorded by Suzuki et al.²⁵ Affected neurons include both central and peripheral populations. Within the neuraxis, neurons of the substantia ni-

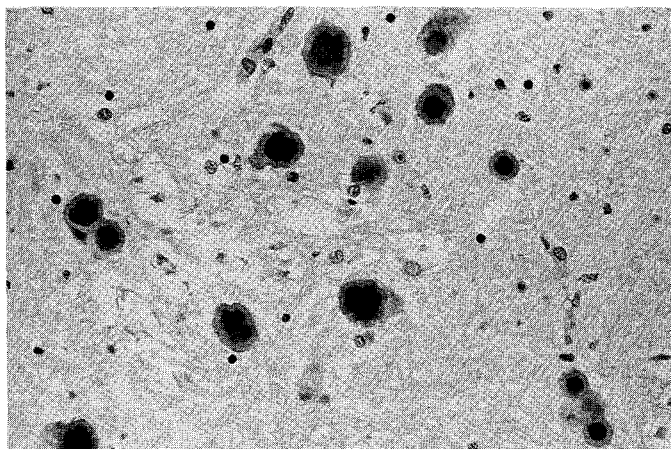


Fig. 1-39. Lafora bodies, dog. Note dense core and radiating peripheral zone. (PAS, $\times 350$.)

gra, pontine nuclei, and piriform lobe are most consistently affected. These structures are by light microscopy round, amphophilic, finely granular bodies and usually single. They are PAS and alcian blue positive and bind the lectin concanavalin A, indicating mannose or glucose residues.²⁶ Their ultrastructural basis is one of regular tubules that amass within the granular endoplasmic reticulum in parallel or jumbled arrays. The Suzuki group suggests that these structures are microtubules. They do not seem to be associated with degeneration of the affected neuronal populations.

Lafora bodies (polyglucosan bodies) are intracytoplasmic neuronal inclusions that occur in the CNS of humans and some animal species. Their presence has been associated with a neurological disorder in the dog that we have discussed elsewhere under the designation neuronal glycoproteinosis. In the dog and cat, these complex glycoprotein bodies are more commonly encountered as an incidental observation with advancing age. They occur throughout the CNS, particularly in the thalamus, tectum of the midbrain, cerebellum and medulla, and the caudal lumbar, sacral, and caudal spinal cord segments.^{15,27,28} They are found within neuronal perikarya, while those within axons may appear to be free in the neuropil. Lafora bodies are ovoid in shape, basophilic, and strongly PAS-positive (Fig. 1-39) and bind the lectin concanavalin A.^{29,30} The feline examples may contain galactose as they are also reactive with peanut agglutinin. Both canine and feline bodies are labelled by a monoclonal antibody to human polyglucosan.³¹ Ultrastructurally, they are an admixture of branching filaments, electron-dense bodies, and glycogen.³² They are encountered in the CNS of a variety of aged animals.³³

Pathologists soon learn to recognize the pale, golden brown, fine, granular cytoplasmic inclusions in neurons, cardiac myocytes, and some other cells that are seen in mature and old animals. This age-associated pigment, which

seems to accumulate without deleterious effects to the cell, is conventionally named **lipofuscin**.^{5,6} In contrast, the substrates that collect in the **ceroid-lipofuscinoses** seem to be cytotoxic and may be associated with considerable neuronal necrosis and even cerebral atrophy.³⁴ Ceroid-lipofuscinosis is discussed with the storage diseases; in sheep, the domestic animal species most fully studied, this inherited disorder involves the storage of proteins that have lipid-like properties and so has been named a proteolipid proteinosis.³⁴ To emphasize the differences between lipofuscin of aging and ceroid-lipofuscinosis, the term **age pigment** is preferred.¹⁴ Finally, pigment in macrophages following lipid degeneration and peroxidation should be designated **ceroid**.

Storage of age pigment can be found in a year-old dog³⁵ and is generalized in the brain by age 4. Depending upon the plane of section, some neurons appear to be unaffected, as storage is often polar, involving the perikaryon between the nucleus and the axon hillock. Heavier aggregates produce a perinuclear to diffuse accumulation in the cytoplasm. Characteristically, not all neuronal populations are prone to develop aging pigment. For example, canine cerebellar Purkinje cells and neurons of the dorsal motor nucleus of the vagus seem to be refractory. In contrast, neurons of the hypoglossal and oculomotor nuclei are consistently affected between 2 and 3 years of age. Other populations have an intermediate level of pigment. Senescent mice and rats show most storage in the hippocampus.³⁶ In humans, the inferior olivary nucleus is heavily affected from early life.³⁷ Typically with advancing age, heavier pigmentation will be seen in individual neurons, and proportionately more neurons in a nucleus will be affected. Ultrastructural examination reveals storage in astrocytes and oligodendrocytes also. The autofluorescent, histochemical, and electron microscopic features of these pigments are found in the discussion of neuronal ceroid-lipofuscinosis.

LEPTOMENINGES, CHOROID PLEXUS, AND BLOOD VESSELS

Thickening (sclerosis) as a result of **fibrosis** with acellular collagen deposition or hyalinization may be found in the leptomeninges and choroid plexus stroma of old animals, most notably the dog and the horse. Plaques of **osseous metaplasia** are common in the spinal dura mater of old dogs, usually the larger breeds. These grayish islands of lamellar bone may contain adipocytes and myeloid elements. They have been claimed to have clinical significance³⁸ but are purely an incidental, age-related change. An association with intervertebral disk prolapse has been suggested, but this metaplastic change can be found in the cranial dura also. Progressive cholesterol accumulation in the choroid plexuses is an equine idiosyncrasy, the lipid crystals inciting a giant cell reaction or **cholesterol granuloma**. Brownish nodular thickening of the plexuses with glistening white crystals is a common incidental observation in mature and aged horses. Occasionally, deposits

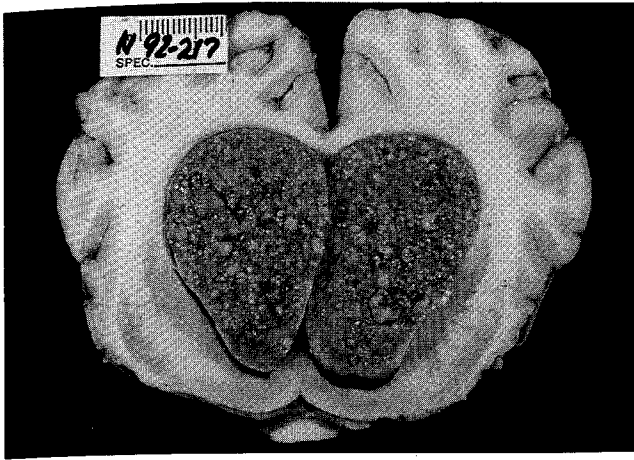


Fig. 1-40. Massive bilateral cholesterol granulomas, choroid plexus of lateral ventricles, horse.



Fig. 1-41. Arteriosclerosis secondary to hypothyroidism, dog. There is a red thrombus in the basilar artery. Focally the basilar artery, arterial circle and its tributaries are thickened and discolored from atheromatous changes (arrows).

in the plexuses of the lateral ventricles are massive and fill the ventricular space (Fig. 1-40), resulting in attenuation of the periventricular white matter from compression or obstruction to CSF flow through the interventricular foramen. Some affected horses have presented with a history of seizures. These cholesterol granulomas appear to result from chronic hemorrhage into the plexus stroma, but the underlying pathogenesis is obscure. Microscopically, there are abundant empty clefts formed by the cholesterol crystals, macrophages, hemosiderin pigment, and fibrosis.



Fig. 1-42. Encrustation of a blood vessel, lentiform nucleus, horse. (H&E, ×350.)

Atherosclerotic vascular degeneration, so important in humans, is largely unknown in veterinary pathology apart from the avian species. Hypothyroid dogs may develop impressive, widespread arterial atherosclerosis including involvement of cerebrospinal vessels (Fig. 1-41), but their vascular disease is usually clinically silent. Retinal vasculopathy is not the problem in diabetic dogs and cats that is the case in humans. Essential hypertension is recognized in the dog³⁹ and may account for some of the sporadic cerebrovascular accidents seen in the mature canine population. Cerebrovascular amyloidosis has been found in aged dogs by investigators willing to search for it. The changes occur progressively with advancing age and are not associated with specific neurological deficits. (This topic is discussed in the following section). Arteriosclerosis with the development of intimal plaques of fibroelastic tissue affects arterial vessels of aged dogs, particularly the left ventricular papillary muscle but also the neuraxis.⁴⁰ These changes appear to be without deleterious effects for the CNS.

Mineralization in the wall of CNS blood vessels is only sporadically encountered in aged animals except for the frequent observation in the equine brain, particularly in the area of the basal nuclei–internal capsule⁴¹ and cerebellar medulla. Affected vessels, which may be arteries, capillaries or veins, are progressively encrusted with calcium and iron salts (Fig. 1-42). In advanced equine cases, vessels are heavily impregnated, and the vascular lumen may be narrowed, but thrombosis or contiguous areas of ischemia are rare.

ALZHEIMER'S DISEASE AND PATHOLOGICAL COMPARISONS IN ANIMALS

Alzheimer's disease is the most common of more than 60 dementing illnesses of humans and accounts for more than half of all forms of dementia.^{42,43} The clinical hallmarks of Alzheimer's disease are the relentless loss of personality and intellectual capacity: memory, reasoning, judgment, and so on. The primary macroscopic finding at autopsy is brain atrophy, which affects cerebrocortical gray and white matter and subcortical nuclei. Neuronal atrophy and loss may be dramatic, for example, 67% of some neocortical populations.⁴⁴ Some of the microscopic changes found in Alzheimer's disease can be found to a lesser degree in the normal aging human brain, in some forms of Parkinson's disease, in mature Down's syndrome patients, in the brains of boxers (pugilistic encephalopathy), and in some chronic viral encephalitides. Thus these changes are not disease-specific, but their frequency and distribution are greatly magnified in the Alzheimer's disease patient.⁴⁵

The cellular changes in Alzheimer brain primarily involve neurons and their processes and are threefold:

1. **Neurofibrillary tangles**, which are flame-shaped or coiled accumulations of argyrophilic, twisted tubules (paired helical filaments) within the perikarya of neurons (Fig. 1-43)
2. **Senile (neuritic) plaques**, which consist of approximately circular focal aggregations of degenerating neurites (nonmyelinated axons and dendrites), processes of reactive microglial and astroglial cells, and a central extracellular amyloid core
3. **Granulovacuolar degeneration** of neuronal somata with small, clear vacuoles sometimes harboring dense granular bodies

Neuronal loss particularly affects areas of the neocortex (especially the temporal lobe), hippocampus, entorhinal cortex, and deep structures such as the nucleus basalis of Meynert, locus ceruleus, and the brain stem raphe nuclei. Neurofibrillary tangles are found particularly in pyramidal cells of the hippocampus, neocortex, amygdala, hypothalamus, and brain stem. Neuritic plaques are found in gray matter of the limbic system and association areas of the hippocampus. The amyloid deposited in the CNS is a unique type designated $\beta/A4$ protein; it is a derivative of a larger molecule.

Similar brain lesions to those found in the Alzheimer patient occur in several animal species with aging.⁴⁶ Senile plaques are common in normal aged rhesus monkeys over 16 to 25 years.^{16,47} It appears that in these primates, neuritic changes precede amyloid deposition,⁴⁸ a crucial question for the disease of humans. Aged bears (genus *Ursus*), including polar and Asiatic brown bears, acquire neurofibrillary tangles and develop senile plaques as they age.⁴⁹ Alzheimer's disease patients commonly have **cerebrovascular amyloidosis** affecting meningeal and cortical vessels.⁴² Amyloid

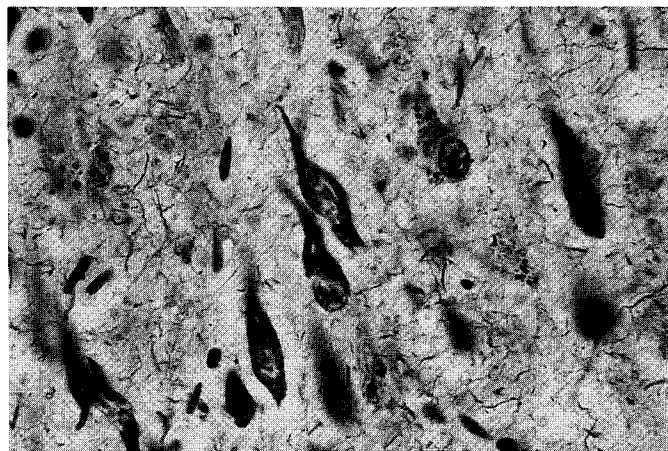


Fig. 1-43. Alzheimer's disease, human. Neurofibrillary tangles in hippocampal neurons. (Bodian, $\times 560$.)

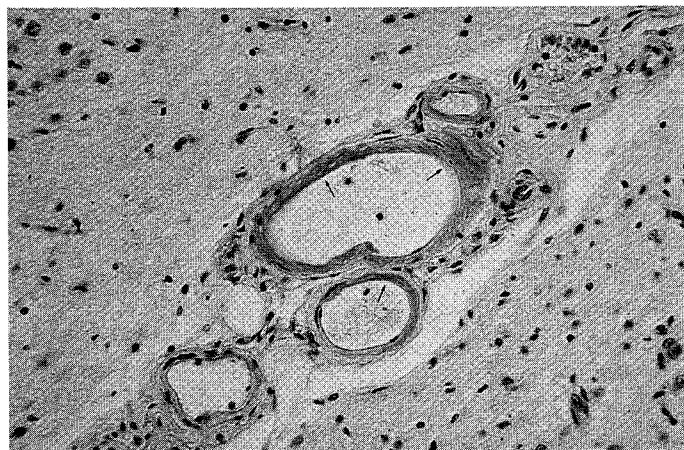


Fig. 1-44. Cerebrovascular amyloid (arrows) identified with Congo red, dog.

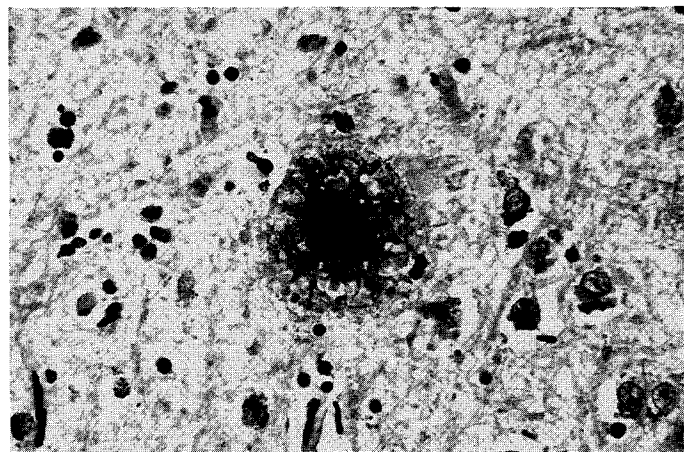


Fig. 1-45. Senile plaque, dog. (Periodic acid methenamine stain.)

deposits in meningeal and cerebral arteries, arterioles, and capillaries can be found in the aged dog (Fig. 1-44),^{50,52} and senile plaques may be demonstrated also (Fig. 1-45).^{5,53} Typically the canine plaques do not have a neuritic halo with a prominent amyloid core and so do not qualify as classical plaques; they have been designated diffuse or primitive plaques.^{54,55} A distinction that separates these aging changes in most animals' brains from the aging process and Alzheimer's disease in humans is the lack of neurofibrillary tangles in animals.

In dogs with leptomenigeal and cortical congophilic angiopathy, an association with cerebral hemorrhage has been suggested.^{51,54} Most of these hemorrhages seem to be clinically inapparent, and only rarely are they large enough to produce signs of cerebral disease.⁵⁶ In some cases, there is no association with cerebral hemorrhage.⁵⁷ Cerebrovascular accidents are encountered sporadically in aged dogs, but that they are a result of amyloid vasculopathy has not been recognized,⁵⁸ whereas several syndromes of cerebrovascular amyloidosis and cerebral hemorrhage occur in humans.

References are on p. 66.

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Chapter 2 MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM

BRAIN

Cerebrum

- Cerebral aplasia
- Encephalocele, meningoencephalocele, meningocele, exencephaly
- Holoencephaly, arhinencephaly, cyclopia
- Agenesis of the corpus callosum
- Hydranencephaly, porencephaly
- Lissencephaly, pachygyria
- Polymicrogyria
- Microencephaly
- Megalencephaly
- Hydrocephalus
- Hydromyelia, syringomyelia
- Miscellaneous

Brain stem

- Diencephalon
- Microphthalmia, anophthalmia, optic nerve hypoplasia, aplasia
- Mesencephalon
- Pons
- Medulla
- Arnold-Chiari malformation

Cerebellum

- Viral infections
- Primary malformations
- Dandy-Walker syndrome

SPINAL CORD

- Meningocele, meningocele
- Diplomyelia, diastematomyelia
- Myelodysplasia
- Miscellaneous

Malformations of the CNS are common.¹⁻³ The major recognized causes include heredity and in utero exposure to infectious agents and other teratogens. Therapeutic agents administered during gestation may be teratogenic.^{4,5} Hyperthermia is an important cause of human birth defects and may be of importance in animals.^{6,7} Many malformations remain unexplained. Malformations that result from in utero

infection (most are viral) are a combination of **hypoplasia** that follows destruction of progenitor cells and **atrophy** from the destructive effect on already differentiated growing tissue. Some viral agents and other teratogens predominantly affect specific sites in the nervous system (e.g., BVD virus in cattle, cerebellum; Akabane virus in ruminants, cerebrum and spinal cord). Others disturb the nervous system diffusely. For reviews of congenital defects of the CNS in calves, see Cho and Leipold,² Leipold and Dennis,⁸ and for pigs, Done.⁹ For reviews of viral teratology, see Johnson,¹⁰ Fuccillo and Sever,¹¹ and Oberst.¹²

This chapter is organized anatomically, based on the site of the major malformation under consideration, which is usually the location of the cause of the clinical signs observed.

Brain

CEREBRUM

Cerebral aplasia (anencephaly, prosencephalic hypoplasia)

Most publications refer to the absence of cerebral hemispheres as **anencephaly**. This is a misnomer as there is still considerable brain tissue present in the reduced cranial cavity. Although many authors recognize this fallacy, they persist in the use of the term.¹³ True anencephaly is rare. **Cerebral aplasia** is most commonly seen in **calves** as a sporadic malformation with no cause defined. Reports in other species are rare.¹⁴ Calves with cerebral aplasia can survive birth and live for a few days if nursed properly. They can stand and walk if the caudal brain stem is not significantly involved. They are profoundly lethargic, stand with their head in the corner of a pen for hours, and are blind, usually with normal pupillary light responses (cerebral blindness).

Despite the absence of cerebral hemispheres, they show some discomfort associated with noxious stimuli to their digits or nasal mucosa. Perception is occurring at the level of the thalamus.

In calves,¹⁵ cerebral aplasia is usually associated with a defect in the calvaria consisting of a small opening on the midline between the frontal bones. Frequently CSF leaks out of this opening where the rostral part of the brain stem attaches to the skin through this opening. The opening on the skull is a small **cranium bifidum**. The calvarial part of the skull is flattened; on removal of the calvaria, there is no cranial cavity for the absent cerebral hemispheres. The only cranial cavity consists of a cylindrical space large enough to accommodate the brain stem and a reduced elongate cerebellum.

Usually there is complete absence of each cerebrum. The diencephalon is attached to the skin rostrally and consists of a mass of parenchyma without its usually distinctive features such as the bulges of the geniculate nuclei or a well-defined interthalamic adhesion. The optic nerves and chiasm are normal with optic tracts on the lateral surface of the diencephalon. The pituitary is normal. There is no internal capsule on the side of the diencephalon and no crus cerebri beneath the mesencephalon. The colliculi of the mesencephalon are not well defined. There are no transverse fibers of the pons. The cerebellum is reduced in size, with greater length than width. There are no pyramids on the ventral surface of the medulla. This description is the most common in our experience, but variations occur in the literature. The eyes and optic nerves may be rudimentary (microphthalmia). Remnants of cerebral hemispheres may persist, intermixed with numerous blood vessels.

We can hypothesize on the pathogenesis of this malformation by considering the early stages of brain formation. In normal development, the neural plate (which is attached to skin ectoderm laterally) folds and fuses to form a neural tube as it breaks away from the overlying skin ectoderm. The rostral opening of the neural tube prior to its closure is called the rostral neuropore. This is at the site of the developing prosencephalon. This most rostral brain vesicle is developing as the fusion process is occurring. Normally the prosencephalon gives rise to two telencephalons by a rostral lateral evagination of a vesicle on each side adjacent to where the rostral neuropore closed. Each telencephalon forms an entire cerebral hemisphere. The remaining component of the prosencephalon becomes the diencephalon of the brain stem. If the neural tube was prevented from fusing rostrally, at the level of the rostral neuropore, the prosencephalon would remain attached to the skin ectoderm at that point. This would expose the neural canal (the subsequent ventricular system) to the skin surface and prevent meninges and bone from developing over the brain at that point. This would account for the opening in the calvaria (the **cranium bifidum**) and the leakage of CSF. This point of attachment is where the telencephalic vesicle normally develops. The

inability of this vesicle to form would result in a failure of the cerebrum to develop. Another theory is that the defect represents a rupture of the neural tube after initial closure, that is, **neuroschisis**.¹⁶ In humans, spina bifida with myelocoele (myeloschisis) commonly accompanies **cranium bifidum** with **anencephaly** (encephaloschisis). In pregnant rats exposed during gestation to excessive levels of Vitamin A or cyclophosphamide, **anencephaly** has been observed in the fetuses to follow an initial **cranium bifidum** and **exencephaly**.^{17,18}

In the absence of cerebral hemispheres, no internal capsule develops. The absence of descending cerebral efferent (projection) neurons in an internal capsule accounts for the absence of crus cerebri and the corticospinal axons in the medullary pyramids. Pontine nuclei and their transverse fibers of the pons and middle cerebellar peduncles are dependent on corticopontine neuronal development, which is absent here. The failure of this system to develop may account for the reduced cerebellar hemispheres. Dysplasia occurs in the malformed diencephalon and mesencephalon and is readily recognized in the haphazard, unorganized development of cortex in the cerebellum. **Anencephaly** has been reported in calves, in which this anomaly is associated with extensive anomalies in the other body systems.¹⁹

In humans, numerous causes have been proposed, with environmental and genetic factors receiving the most emphasis, but in reality most of these malformations have remained unexplained.²⁰ The same is true for domestic animals.

Encephalocele, meningoencephalocele, meningocele, exencephaly

A protrusion of brain tissue through a defect in the calvaria that is still covered by skin is an **encephalocele** or, more accurately, **meningoencephalocele**, as the meninges still cover the protruding neural tissue and attach it to the skin. If only a fluid-filled sac of meninges protruded, this would be a **meningocele**. **Exencephaly** is a protrusion of brain tissue not covered by skin or meninges. **Exencephaly** is rare, usually is associated with severe skull as well as brain malformation, and results from failure of the neural plate to separate from the skin ectoderm and fuse into a neural tube. Excess vitamin A administered to pregnant mice during neurulation consistently causes **exencephaly** by its direct effect on the neuroepithelium.²¹

Encephalocele and **meningocele** are inherited in **pigs**.²²⁻²⁴ **Encephalocele** is inherited in **Burmese cats** and also is associated with presumed teratogenicity of griseofulvin administered to the pregnant queen throughout a significant period of gestation.^{4,25} In most of these, the neural tube has closed properly and the two cerebral hemispheres have developed but failed to separate from the skin ectoderm so that the intramembranous ossification that gives rise to most of the calvaria has been severely inhibited, creating the usually large skull defect that allows the brain to protrude.

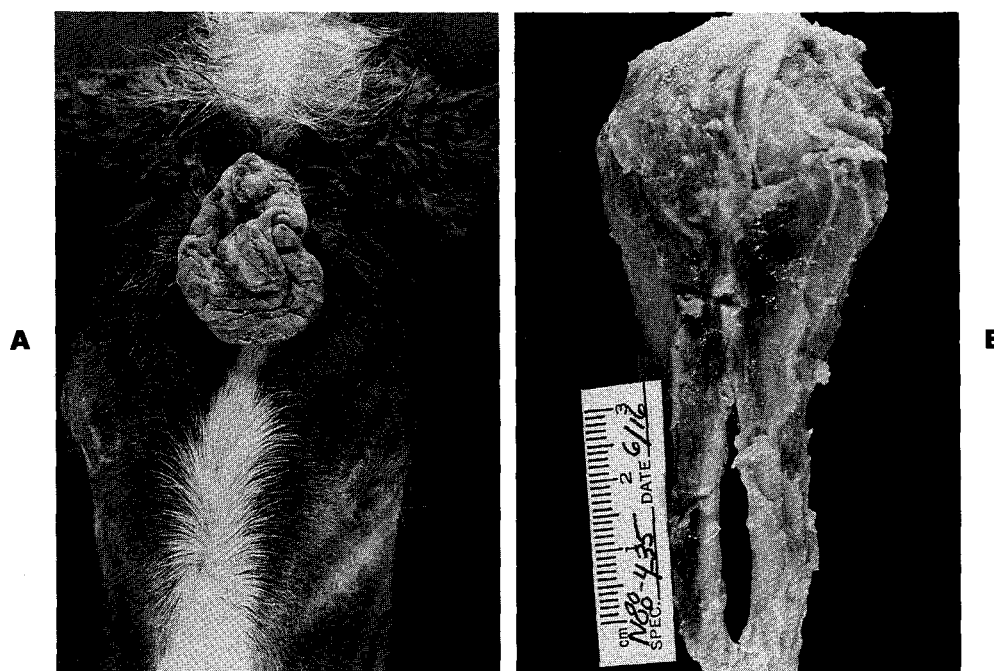


Fig. 2-1. A, Meningoencephalocele, foal. B, The associated cranium bifidum.

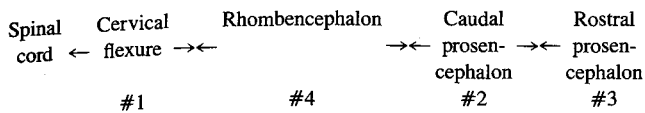
Often the lateral ventricles are dilated, which increases the volume of protruded tissue. Although most of these involve the telencephalon and frontal or frontoparietal bones, a few occur caudally, involving the occipital bones and rhombencephalon.

Beware that in dogs there is considerable variation in size of the foramen magnum from the amount of occipital bone ossification that occurs. In brachycephalic toy breeds, there can be a significant enlargement of the foramen magnum dorsally, exposing the cerebellar vermis. However, the latter is not abnormally protruded and is covered by a membrane between the edges of the adjacent occipital bones. This has been referred to as occipital dysplasia but is a normal breed variation in ossification.^{26,26a}

In the strain of **Burmese cat** known as the Eastern or contemporary "new look" strain, there is a **craniofacial malformation** inherited as an autosomal dominant with incomplete expression.^{25,27,28} The osseous cranial cavity is widely open dorsally, allowing the brain to protrude covered by skin. This encephalocele consists mostly of cerebral hemispheres often enlarged from dilated lateral ventricles. The eyes and optic nerves are rudimentary (microphthalmia) and the upper face-jaw is severely malformed. Most kittens lack the incisive, ethmoid, and nasal bones. The maxillary bones are shortened and duplicated, including the lateral palatine processes. The palate is closed but widened. Associated with this maxillary duplication are two philtrums and four sets of whisker pads instead of two.

We observed an unusual meningoencephalocele in a **Belgian foal**. The foal was born dead with a flattened skull in the region of the cranial cavity where a 5- by-10-cm mass

of nonhaired pink tissue protruded through a narrow elongate defect between the parietal bones (Fig. 2-1). This protruded tissue extended through the cranium bifidum, where it was continuous with a rudimentary mesencephalon that was deflected toward the calvarial defect. There was extensive bilateral cerebral hypoplasia. Each cerebrum consisted of a small tubular mass of parenchyma attached to a mass of midline tissue presumed to be the diencephalon. Normal eyes and optic nerves were associated with the latter. Caudal to the diencephalon, the neural parenchyma of the presumptive mesencephalon was extremely reduced, almost membranous in quality. This deviated dorsally and extended out through the calvarial defect, where it was attached to an area of nonhaired skin. The rudimentary mesencephalon then continued caudally to a small pons and medulla covered by a hypoplastic cerebellum. Studies in the mouse show a consistent sequence of four points of fusion that by extension close the neural tube where the brain will form.^{29,30} The first fusion occurs at the cervical flexure and extends caudally to form the spinal cord neural tube and rostrally over the myelencephalon to meet the fourth fusion site. The second fusion site begins over the caudal prosencephalon region and extends rostrally to meet the fusion from the third site that is progressing caudally from the most rostral part of the prosencephalon. The second fusion site extends caudally over the mesencephalon to meet the rostrally extending fusion from the fourth site over the rhombencephalon. The closure of the mesencephalon and separation from skin ectoderm relates to the union of the second and fourth fusion sites. If this is aberrant, it could account for the unique site of the encephalocele in this foal.



We have observed two large **lipomeningoceles** in a Holstein cow, and one has been described in an Angus.³¹ In this Holstein, one lipomeningocele protruded through a midline elongate defect in the calvaria (cranium bifidum) and consisted of a skin-covered, soft, pedunculated mass of adipose tissue that measured about 8 cm in diameter (Fig. 2-2). It was continuous with a long cylindrical cord of lipid tissue that extended into the longitudinal cerebral fissure and blended with the falx cerebri of the meninges. The other lipomeningocele was similar in size, a pedunculated mass on the midline dorsal to the sixth thoracic vertebra. The cylindrical stalk of adipose tissue extended ventrally into a bony groove formed on the caudal aspect of a partially duplicated spine of T6. Here the lipid mass was continuous with a hollow, tubelike extension of the connective tissue that covers the inside of the vertebral arch (periosteum) and the inner surface of the adjacent yellow ligament. A catheter placed in the epidural space could be passed dorsally through the lumen of this tube to the overlying lipid mass. Although this sheet of connective tissue was separated from the dura surrounding the spinal cord by the epidural space, both layers are thought to have a common embryonic origin, and this malformation is a form of meningocele. In the cranial cavity, there is no epidural space, and the dura serves as a covering for the brain as well as the periosteum for the adjacent bones. These are called lipomeningoceles³¹ because of the association of the mass of lipid with an extension of meninges through a defect in their bony covering to the skin. In this Holstein, these mass lesions were present at birth as small soft swellings. At slaughter 3 years later, they had only grown a small amount, commensurate with the accumulation of lipid and overall growth of the cow. There were no associated parenchymal nervous system lesions and therefore no clinical signs observed with these.

Holoencephaly, arhinencephaly, cyclopia

This malformation is most common in sheep and occurs when pregnant ewes graze on *Veratrum californicum* during the fourteenth day of gestation.^{32,33} A teratogenic steroidal alkaloid absorbed from this plant crosses the placenta and inhibits the ventral aspect of the developing prosencephalon prior to the development of optic vesicles.³⁴ Normally a single ventral region of prosencephalic neuroectoderm is responsible for initiating the development of the eyes. Interaction between this originally single "eye field" and the underlying head mesenchyme and foregut endoderm is responsible for its separation into two symmetrical eyefields that bulge out as the optic pits and vesicles. The same interaction is responsible for the development of two separate dorsolateral telencephalic vesicles. This plant alkaloid interferes with this interaction, resulting in the development



Fig. 2-2. A, Lipomeningocele, cow. B, Lipomeningocele viewed from the ventral surface of this cow's brain.

of a single optic vesicle and thus a single, median-positioned eye (**cyclopia**) and usually a single, nondivided cerebrum (**holoencephaly**). This single, saclike cerebral structure is continuous across the midline over the diencephalon. Cerebral cortical tissue is continuous here but not via a corpus callosum. As a rule, there is no development of the olfactory components of the brain (**arhinencephaly**). Usually the brain stem and cerebellum are normal. Associated with the prosencephalic malformation is extensive facial deformity. A single midline orbit forms around the eye, but no nasal cavities develop or ethmoid, nasal, or incisive bones. Usually a soft tissue appendage (proboscis) is situated above the eye.

A similar cyclopic malformation of unknown cause occurs sporadically in other species.³⁵ This malformation is common in **pigs**.^{36,37} It has been observed once in a kitten born from a queen treated with griseofulvin for a considerable portion of the gestation.⁴ We have observed it in both heads of a conjoined pair of twins in the Siamese breed. These were fused throughout the head, neck, and thorax region (**craniothoracopagus**).

Occasionally two separate or partially fused eyes occur

in the single median orbit. If there are two eyes in separate orbits but still located on the median plane, the malformation is called **cebocephaly** (monkey face). This is a less severe expression of the same embryological defect.

Holoencephaly is usually referred to as **holoprosencephaly** in the veterinary literature, but the primary malformation involves only the formation of a single telencephalon: one cerebrum with neocortex continuous across the midline. In some publications, the same telencephalic anomaly is called **arhinencephaly** because of the constant failure of the olfactory system to develop.³⁸ However, the latter can occur without holoencephaly. In holoencephalic brains, the diencephalon is usually normal or manifests only secondary changes. This formation of a single telencephalic vesicle is accompanied by an absence of a rostral commissure and corpus callosum (the neocortical interhemispheric commissure), septum pellucidum, septal nuclei, and the olfactory system (arhinencephaly)—bulbs, peduncles, and cortex.³⁹

Holoencephaly can occur without the cyclopic malformation but is commonly associated with some degree of facial malformation. In children, a graded series of facial anomalies occurs with holoencephaly.⁴⁰ Causes in humans include various forms of inheritance and chromosomal abnormalities.⁴¹ No environmental teratogen has been implicated. Holoencephaly with or without cyclopia has been reported in **pigs**^{42,43} and **calves**.⁴⁴ A possible autosomal recessive inheritance has been observed in **Border Leicester lambs**.⁴⁵

Agenesis of the corpus callosum

Agenesis of the corpus callosum occurs sporadically as an isolated anomaly in which both telencephalic vesicles develop into the two cerebral hemispheres, but this commissure that normally develops in the lamina terminalis between the neocortex of each hemisphere fails to form.^{46,47} The septum pellucidum is absent, as well as the hippocampal commissure that connects the archicortex of each hemisphere. The cause is unknown, and no specific clinical neurologic abnormality has been associated with it. Other malformations of the CNS or other body systems may accompany it.⁴⁸ Aplasia or hypoplasia of the corpus callosum is a consistent feature of the unique axonopathy of Labrador Retriever dogs (Fig. 2-3). Failure of this tract to develop presumably reflects a particular susceptibility of these axons—or the radial astrocytes that guide them—to the undefined deficit in this disorder.

Hydranencephaly, porencephaly

These malformations represent different degrees of destruction and failure of development of primarily the neopallial part of the telencephalon. In **hydranencephaly**, there is nearly complete destruction and lack of development of the neocortex with sparing of the paleopallium-olfactory components, the archipallium-hippocampus, fornix, and also the basal nuclei (Fig 2-4). Usually all that remains of

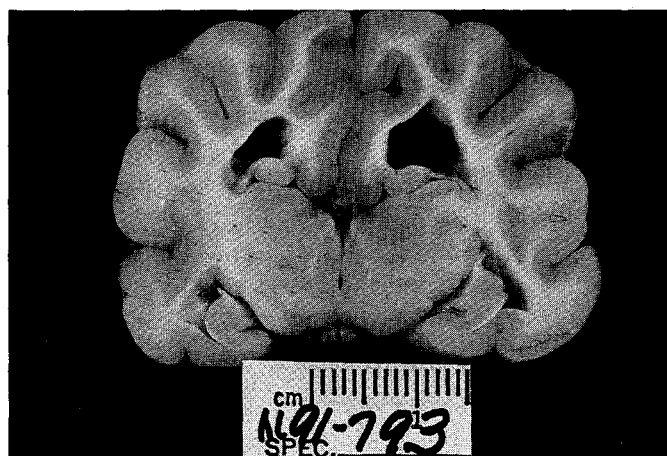


Fig. 2-3. Aplasia of the corpus callosum, Labrador Retriever dog.

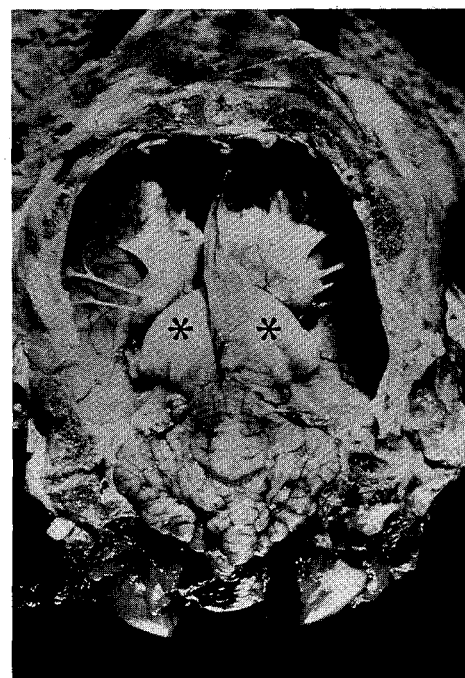


Fig. 2-4. Hydranencephaly, calf. Destruction of neopallium with preservation of hippocampi (asterisks) and basal nuclei. Cerebellum is intact.

the neopallium is a thin, nearly transparent membrane that collapses on the underlying brain tissue when the brain is removed. This membrane consists mostly of astroglia, and pia mater, and a few blood vessels. The lateral ventricles are extensively dilated and filled with CSF to take up the space not occupied by cerebral tissue. The choroid plexus is normal. This lesion is thought to result from destruction of the ventricular (germinal) zone of the telencephalon as well as the neocortex that is already formed. The lesion

therefore represents both hypoplasia and secondary atrophy. The brain stem and cerebellum are usually normal. Occasionally cerebellar hypoplasia and atrophy also occur. The cranial cavity usually is of normal size with an intact calvaria that is not abnormally dome-shaped.

When hydranencephaly is not accompanied by other brain lesions, the clinical signs reflect the extensive loss of cerebral tissue: lethargy, propulsive circling, head pressing, and blindness with normal pupillary responses to light. The gait is reasonably normal with occasional minimal ataxia. When cerebellar lesions also occur, the neonate may be unable to orient itself to stand or will walk with a severe cerebellar ataxia: hypermetria, spasticity, and loss of balance. The most common cause is a viral infection of the fetus during gestation. Examples include the **Akabane virus** in ruminants in Australia,⁴⁹⁻⁵⁴ Japan,⁵⁵⁻⁵⁷ and Israel;^{58,59} the **Bluetongue virus** in sheep and cattle in North America;⁶⁰⁻⁶⁶ the **Rift Valley fever virus** and the virus of **Wesselsbron disease** in sheep and cattle in Africa;^{67,68} and the **Cache Valley virus** in sheep in the United States.⁶⁹⁻⁷¹ In Japan, the **Chuzan virus** (genus *Orbivirus*) has been implicated in the production of hydranencephaly and cerebellar hypoplasia in calves.⁷²⁻⁷⁵ Rarely, the **bovine virus diarrhea** and **Border disease virus** produce this lesion in calves and lambs, respectively. Hydranencephaly is a rare lesion observed in kittens affected by the **panleukopenia virus**.⁷⁶ The period of susceptibility at which infection of the fetal brain leads to hydranencephaly varies with the agent and the host. Some infections at earlier points of embryonic development are lethal, whereas later in gestation susceptibility has passed with progressing CNS differentiation. With late infection, the fetus mounts a fairly conventional inflammatory reaction, and development may not be impeded. Experimental infection of pregnant ewes with the Border disease virus beyond day 80 of gestation resulted in polyarteritis in the lambs.⁷⁷

If the infection occurs later in the period of vulnerability or is less destructive to the developing brain, the insult produces cystic cavities in the cerebrum, primarily the neopallial part. This is known as **porencephaly**. These cavities (pores) may communicate with the lateral ventricle or subarachnoid space. They are usually multiple, bilateral, and randomly located; however, individual cavities can occur (Fig. 2-5). Hydranencephaly or porencephaly also occurs in some lambs with in utero copper deficiency (swayback).⁷⁸ Hydranencephaly of remarkable severity is also the hallmark of a syndrome of prolonged gestation that affects sheep in Scotland.⁷⁹ The cause is not known.

At birth, the viral inflammation that occurred during gestation will have subsided, leaving the scarred remains of malformed and atrophied tissue. The collapsed cerebral membrane in hydranencephaly consists of astrocytes, pia, and an occasional inflammatory cell. In porencephaly, the cavities are lined by astrocytes and occasionally accumulations of hemosiderin-filled macrophages. Around some

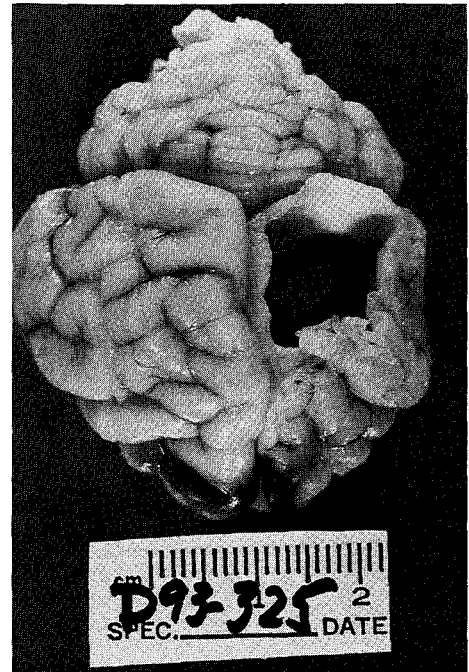


Fig. 2-5. Porencephaly, cat.

cavities there may be remains of the inciting inflammatory lesion with lymphocytic perivascular cuffs, gliosis, and occasionally mineralization of degenerate material.

Arthrogryposis (which means crooked or curved joints but is used to indicate joint fixation) often occurs in these neonates with hydranencephaly. In Akabane viral infections, it is the result of denervation and failure of muscle development due to a loss of cell bodies in the ventral gray column of the spinal cord intumescences.^{80,81} In animals with arthrogryposis from other causes, a depletion of motor neurons in the ventral gray column of the spinal cord is also found.^{82,83} Hydranencephaly and arthrogryposis have been observed as an outbreak in lambs and calves where a viral cause was suspected but not identified.^{84,85}

Lissencephaly, pachygyria

The abnormality in which the cerebrum has a smooth surface without the development of gyri and sulci is **lissencephaly** (Fig. 2-6). This is abnormal in all domestic animals but normal in some laboratory animals (mouse, rat, rabbit) and birds. The lesion involves only the neopallium. The lateral rhinal sulcus is preserved between the smooth neopallium and olfactory paleopallium. The hippocampal archipallium is also normal. In partially affected brains, the sulci are present ventrolaterally in the temporal lobe area of the cerebrum. On transverse section, the neocortex is much thicker than normal (**pachygyria**). The normal laminar pattern of neuronal cell body organization is disrupted. There is no development of corona radiata extending out from the fusion of corpus callosum and internal capsule.

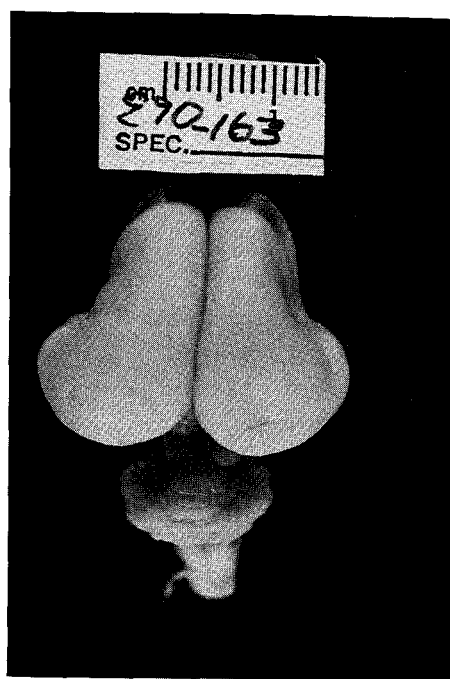


Fig. 2-6. Lissencephaly, Korat kitten.

Bundles of white matter are randomly scattered through the thick cortex including the superficial molecular layer.

In the occurrence of lissencephaly, there is a breed predisposition in the **Lhasa Apso**.⁸⁶ These dogs usually behave normally but are difficult to train; furthermore, seizures often begin around 1 year of age. We have also observed this lesion in a litter of **Wire Fox Terriers** and a litter of **Irish Setters** with cerebellar ataxia from an accompanying severe cerebellar hypoplasia and dysplasia. We have observed lissencephaly with microencephaly in the **Korat** breed of cats; it was associated with abnormal behavior including self-mutilation.

The developmental mechanism normally responsible for gyral formation that is altered in these animals is unknown. A genetic basis is presumed. Lissencephaly has not been observed with other brain lesions that result from in utero infections; where it occurs with cerebellar hypoplasia, the cerebellar lesion is unlike those that result from infection. In humans, microencephaly and anomalies of other body systems may accompany the lissencephaly (agyria-pachygyria). The brain lesion is presumed to result from an arrest of migration of neurons during development. A genetic basis has been proposed for some cases.⁸⁷ In others, an in utero hypoxia or perfusion failure has been suggested.⁸⁸

Polymicrogyria

Polymicrogyria is an excessive production of smaller gyri. It is a rare malformation with unknown pathogenesis that usually accompanies a more extensive brain malformation. In calves, this lesion may be difficult to recognize

because of the normally abundant development of gyri.

An extensive brain malformation occurs in **polled Hereford calves** that are born unable to get up, blind, depressed, and disoriented.^{89,90} Ocular lesions include severe cataracts, retinal dysplasia and detachment, and small optic nerves. Brain abnormalities include polymicrogyria, extensive hydrocephalus, a dorsal flexure of the mesencephalon with fusion of the rostral colliculi and stenosis of the aqueduct, and cerebellar hypoplasia and dysplasia. There is also a diffuse myopathy. This disorder is inherited as an autosomal recessive trait.⁹¹ This constellation of brain lesions has been termed Hereford syndrome 1 and is recognized predominantly in western North America.

Congenital polymicrogyria has been reported in **Murray Grey calves** born blind, disoriented, and either unable to get up or severely ataxic.⁹² The polymicrogyria was variable. Affected gyri were shrunken, wrinkled, and pitted and covered by a hypervascular leptomeninges. A genetic basis was presumed but not proven.

Polymicrogyria and asymmetrical hydrocephalus affecting the lateral ventricles have been seen by T. Van Winkle and others^{92a} in **standard Poodle dogs** and in a **Golden Retriever dog**. Affected Poodles were blind, probably because of the malformation involving the visual cortex, and were euthanized between 5 and 9 months of age.

Microencephaly

An overall reduction in the size of the brain is **microencephaly**. This is especially evident in the cerebral hemispheres. This abnormality is usually one of the numerous manifestations of in utero viral-induced inflammation and has been observed in ruminant fetuses infected with the Akabane virus, bovine virus diarrhea virus, Border disease virus, and Cache Valley virus. It occurs in pigs from the hog cholera virus. Outbreaks have occurred in lambs where microencephaly was the primary lesion and the presumptive infectious agent was not identified.⁹³ Affected lambs are usually born either dead or recumbent with diffuse tremors and no vision.

Megalencephaly

In humans, **megalencephaly** is defined as a brain volume that exceeds the mean by more than twice the standard deviation.⁹⁴ Three subgroups of this malformation are anatomic, metabolic, and dynamic. Dynamic megalencephaly is the brain enlargement that occurs secondary to obstructive hydrocephalus. Metabolic megalencephaly is seen in some of the storage diseases in children. Anatomic megalencephaly results from a neurodevelopmental disorder with excessive neuronal development or decreased normal programmed neuronal death. Genetic causes have been recognized in children. Head enlargement often accompanies the megalencephaly.⁹⁵

Megalencephaly as a primary developmental anomaly is rarely reported in veterinary medicine. With the variation

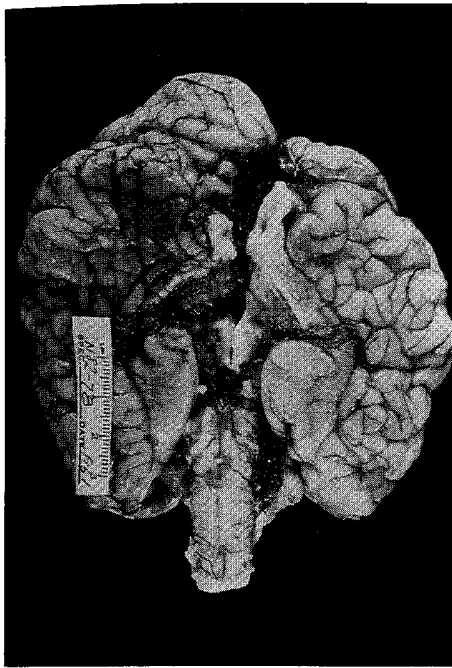


Fig. 2-7. Megalencephaly, calf.

in size of the different domestic animals, minor degrees of this change could be easily overlooked. Megalencephaly commonly occurs secondary to obstructive hydrocephalus. We observed a form of megalencephaly as one of a plethora of anomalies in a **Jersey calf**. In this calf, there was partial duplication of one cerebrum causing gross brain enlargement (Fig. 2-7).

Hydrocephalus

Hydrocephalus is an increase in volume of CSF. Two basic mechanisms cause CSF to increase in volume: compensatory and obstructive. In **compensatory hydrocephalus**, the CSF increases in volume to take up the space where parenchyma has been destroyed, failed to develop, or both. Congenital examples of this are hydranencephaly and cerebellar hypoplasia and atrophy. Acquired examples include parenchymal destruction secondary to injuries and vascular compromise (infarction). In **obstructive hydrocephalus**, the CSF accumulates in front of some obstruction to its normal circulatory pattern or at its site of resorption into the venous system. The most critical component of the pathway of CSF circulation is the mesencephalic aqueduct, and it is the most common site of malformation that causes obstructive hydrocephalus. Aqueductal stenosis is the most common malformation. This is often associated with a fusion of the two rostral colliculi (Fig. 2-8). Sometimes aberrant development—aqueductal forking—accompanies the stenosis. Rarely the aqueduct fails to form. Aqueductal stenosis can also follow prenatal or postnatal inflammations that affect the ependymal surface of the aqueduct.

Because of the aqueductal stenosis, CSF produced by the choroid plexuses of the lateral and third ventricles accumulates in these ventricles. The third ventricle has a limited capacity for dilation because of the thick walls of the diencephalon. Often the interthalamic adhesion fails to develop. The lateral ventricles can be extensively dilated, primarily at the expense of the neopallium. Even with extreme dilation, usually a thin mantle of cortex and white matter are evident in the atrophied, compressed neopallium. As a rule, the loss of white matter from distension and atrophy is more severe than the gray matter loss. Rarely, local areas of destruction of the neopallium occur, creating a hydranencephalic lesion. The paleopallium and basal nuclei are usually spared. There may be extensive expansion of the extension of the lateral ventricle in the frontal lobe into the olfactory peduncle and bulb. This is especially evident in large animals. The hippocampus and its fornix persist ventrally in the lateral ventricle but are often stretched out, especially the fornix and hippocampal commissure. Dorsally, the corpus callosum is usually extensively atrophied, and the septum pellucidum that normally attaches the corpus callosum to the body of the fornix and separates the lateral ventricles is absent. The choroid plexus is visible ventrally in the groove between the caudate nucleus and thalamus and the lateral edge of the crus and body of the fornix. Occasionally, extensive fissures occur in the attenuated white matter of the internal capsule on the inner surface of the thinned neopallium. This is often associated with a yellow-brown discoloration from prior hemorrhage. This disruption is assumed to be traumatic and suggests the low threshold that this atrophic neopallium has to minor external trauma. Possibly it could reflect a sudden increase in CSF pressure.

Less commonly, obstruction to CSF flow occurs at the lateral apertures where CSF normally passes from the ventricular system to the subarachnoid space. This represents a persistence of the neuroepithelial roof plate of the caudal medullary velum that fails to break down to form the apertures just caudal to the cerebellar peduncles. In addition to the widely dilated lateral ventricles and dilated third ventricle, this obstruction causes dilation of the fourth ventricle with mild flattening of the pons and medulla and extensive compression of the cerebellum over the dorsal extension of the fourth ventricle into the center of the vermis. This causes thinning of the vermis and hemispheres. The increased intraventricular pressure may also distend the central canal in the spinal cord to produce hydromyelia. In the cervical spinal cord, an extensive syringomyelia in the dorsal funiculi may accompany the hydromyelia. It is assumed that all this relates to the increased pressure and that at some point the syrinx communicates with the hydromyelia, but this is often difficult to find. This syrinx can be extensive enough to cause gross expansion of the affected cervical spinal cord segments with a soft, fluctuating dorsal surface due to the fluid in the syrinx. For some unknown reason, the first

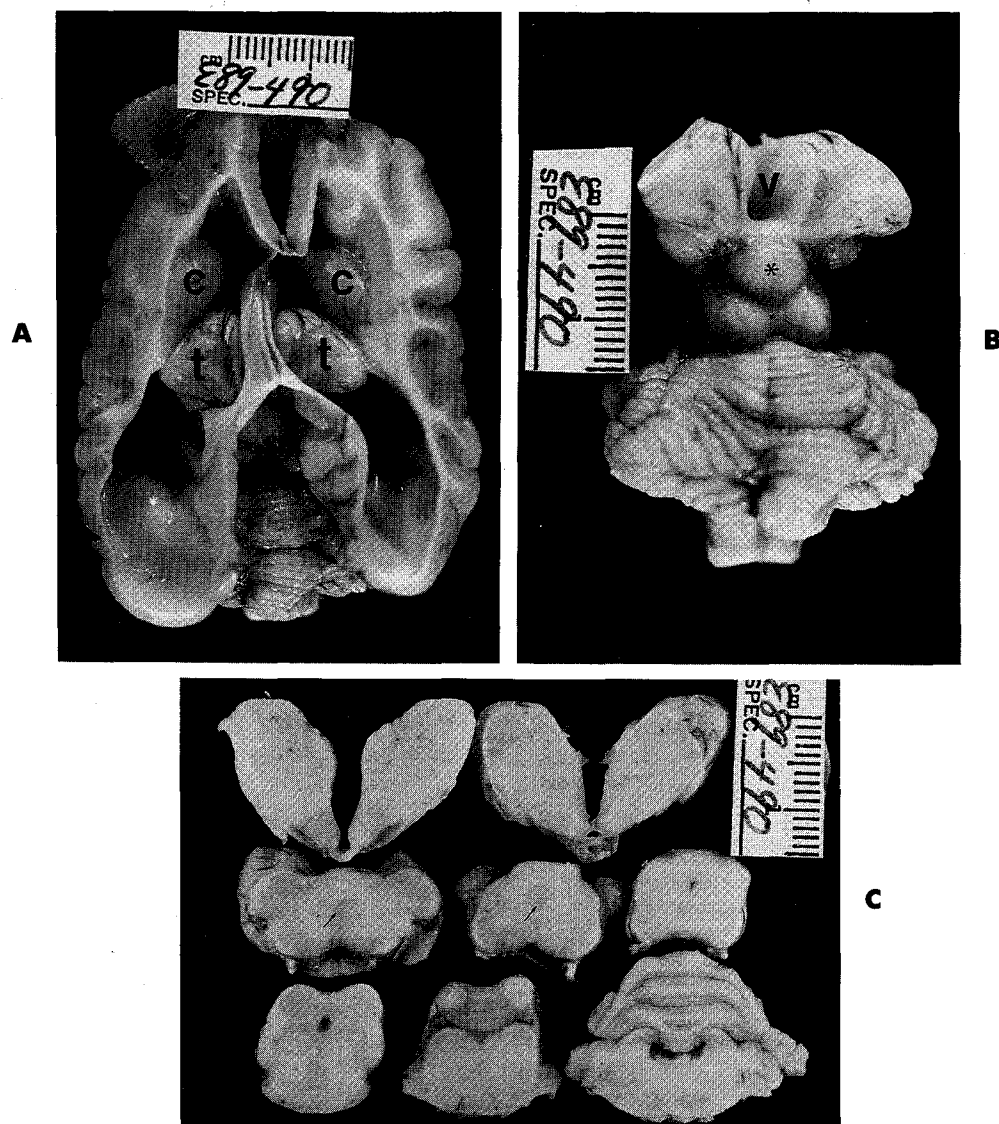


Fig. 2-8. Hydrocephalus, dog (9-week-old pup). **A**, Horizontal section through cerebrum reveals dilation of the lateral ventricles, most pronounced in the occipital lobe. Caudate nuclei (*c*), thalamus (*t*). **B**, Fused rostral colliculi (*asterisk*) and dilated third ventricle (*V*). **C**, Brain stem. Arrows indicate stenotic mesencephalic aqueduct below fused rostral colliculi.

cervical spinal cord segment may be spared from these lesions that develop caudal to it.

As a rule, because of the membranous nature of the tissues at the lateral aperture, this obstruction cannot be seen at autopsy. Similarly, if the disturbance to flow is at the level of the venous absorption of CSF—arachnoid villi/granulations—this also cannot be readily observed at autopsy. For this reason, it is useful to perform a contrast ventriculogram prior to autopsy. This can be performed on the patient immediately after euthanasia. A needle is placed into the dilated lateral ventricle, and radiopaque contrast medium is injected. In normal animals and animals with obstruction at the site of venous absorption, the contrast medium circulates through the ventricular system, passes

through the lateral apertures and caudally along the spinal cord, and produces a normal myelogram. No myelogram is observed with aqueductal or aperture obstruction. The presence or absence of contrast in the fourth ventricle differentiates between aperture or aqueductal obstruction. When the obstruction is presumed to be at the level of venous absorption, it is not known whether this is due to malformed arachnoid villi or to insufficient numbers of them. In vitamin A deficiency in calves that occurs postnatally, morphological lesions have been observed in the arachnoid villi that impair CSF absorption and cause an increase in CSF pressure. This pressure elevation correlates directly with the degree of vitamin A deficiency.^{96,97} The many neuropathological effects of hydrocephalus, including mechanical distortion and im-

paired vascular perfusion, have been reviewed.⁹⁸

Congenital hydrocephalus is more common in **toy breeds of dogs** but occurs in all breeds. The breeds considered to be at risk for hydrocephalus are Maltese, Yorkshire Terrier, English Bulldog, Chihuahua, Lhasa Apso, Pomeranian, Toy Poodle, Cairn Terrier, Boston Terrier, Pug, and Pekingese.⁹⁹ The most common cause is an aqueductal stenosis associated with fused rostral colliculi. This is presumed to be a primary malformation in dogs and cats. It occurs sporadically with no specific pattern of inheritance identified. Other cases that have no observable abnormalities other than the dilated ventricles and no obstruction observed on ventriculography are assumed to have an abnormality in structure and/or function of the arachnoid villi. Its pathogenesis is unknown.

In congenital hydrocephalus, the cranial cavity is usually increased in size, primarily by expansion of the calvaria with lack of ossification and fusion between bones on the dorsal midline and laterally. Occasionally, focal areas of the occipital and temporal bones fail to ossify. The presence and degree of cranial cavity expansion depend on the extent of the obstruction and the time period when it occurs. Extensive hydrocephalus can occur postnatally with no expansion of the cranial cavity. Be aware that toy breeds often have a small palpable midline frontoparietal fontanelle where these bones failed to fuse but have no hydrocephalus. This fontanelle is also referred to as a molera. Small molera are accepted in the published breed standard for the Chihuahua breed.

As well as being a developmental disorder, aqueductal stenosis can occur from prenatal or perinatal viral infection. Hydrocephalus has occasionally been observed in kittens with cerebellar hypoplasia-atrophy due to perinatal feline panleukopenia infection.¹⁰⁰ Experimental intracerebral inoculation of canine parainfluenza virus into 6-day-old puppies caused acute encephalitis and subsequent hydrocephalus due to aqueductal stenosis.¹⁰¹ By the time hydrocephalus occurs, there may be no evidence of inflammation related to the stenotic aqueduct. A suppurative periventricular encephalitis and hydrocephalus has been reported in young dogs (6 to 16 weeks old).¹⁰²⁻¹⁰⁴ All ventricles were dilated. A striking feature was the multiple dissecting diverticula that extended from the dilated ventricles into the adjacent white matter. These porencephalic cavities were not lined by ependyma. The walls of the ventricles and these diverticula were often irregular and discolored brown to orange. Occasionally hemorrhage was seen in the ventricles. Inflammation varied from mild perivascular cuffs and small blood vessel hyperplasia-hypertrophy to diffuse extensive infiltration of parenchyma with neutrophils, mononuclear cells, and macrophages. The latter often contained hemosiderin. Suppurative choroiditis also occurred. No organisms have been observed in the tissues or cultured. Both viral and bacterial causes have been suggested.

Varying degrees of dilation of the lateral ventricles are

a common finding at autopsy of dogs that have no signs of neurological disturbance.¹⁰⁵ Some of these have subclinical evidence of nonsuppurative meningoencephalitis.

Congenital hydrocephalus is common in **calves**, where inheritance has been implicated in numerous outbreaks.^{2,106-108} Stenosis of the mesencephalic aqueduct is a common finding in some of these calves. In some breeds, the hydrocephalus is associated with a specific group of other brain, ocular, and muscle abnormalities comprising specific syndromes.^{89,90} Obstructive hydrocephalus secondary to viral infections of the fetus have not been reported. Congenital hydrocephalus in **foals** is sporadic but can produce a massive enlargement of the cranium with large areas of unossified calvarial tissue.¹⁰⁹

In specific strains of **rats** and **mice**, an inherited hydrocephalus has been recognized in which the mesencephalic aqueduct is not patent or is stenotic.^{110,111} In mice, abnormalities have been recognized in the basal lamina of the neuroepithelium as early as the eleventh fetal day.¹¹² In rats, the abnormal aqueducts were lined by ependymal cells displaced ventrally by thickening of the overlying mesencephalic tectum from abnormal development. Similar aqueductal abnormalities occur in laboratory animal fetuses exposed to folic acid analogs or vitamin B₁₂ deficiency.¹¹¹

Postnatal inflammations that obstruct these same sites of CSF flow and absorption can lead to **secondary obstructive hydrocephalus**. Suppurative bacterial meningitis with or without ependymitis is an occasional cause in young animals. The feline infectious peritonitis coronavirus primarily affects ependymal and leptomeningeal surfaces and often damages the aqueduct, which may result in obstruction and secondary hydrocephalus.

Hydromyelia, syringomyelia

In some dogs with congenital hydrocephalus, there is an associated **hydromyelia** (dilation of the central canal) (Fig. 2-9) and **syringomyelia** (cavitation of the spinal cord parenchyma). The latter occurs most commonly in the center of the dorsal funiculi but also may extend bilaterally into the medial portions of the dorsal gray columns. The latter may occur without the funicular lesion. This is most prominent in the cervical spinal cord, where it often spares the first one or two segments, but it also occurs to varying degrees in segments of the thoracic and lumbar spinal cord. On microscopic examination, there is little evidence of an inflammatory or glial reaction. The cavity is lined by astrocytes or the frayed fringes of the torn parenchyma. These lesions are consistent with physical destruction of the spinal cord associated with CSF buildup, rupture from the dilated central canal, and dissection of the adjacent parenchyma. These spinal cord lesions are more common when the obstruction to CSF circulation involves the lateral apertures. It is assumed that the increased intraventricular pressure is continuous caudally in the central canal, resulting in the hydromyelia as a hydrodynamic compensation. Rupture of

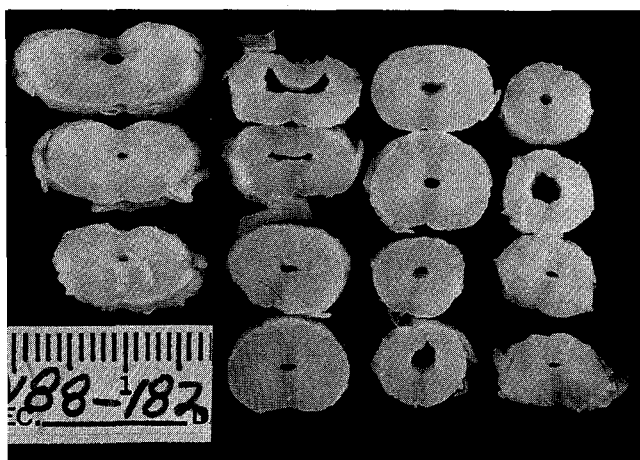


Fig. 2-9. Hydromyelia, dog. The dog was also hydrocephalic. The primary lesion was an olfactory bulb meningioma.

the dilated central canal dorsally into the dorsal funiculi and adjacent gray matter would account for the syrinx formation. However, the communication of the hydromyelia with the syrinx is often difficult to find. Another consideration is that the syrinx is a result of edema accumulating in the dorsal funiculi secondary to the hydromyelia. This lesion is common in children.¹¹³⁻¹¹⁵ Similar spinal cord lesions have been produced experimentally in dogs and cats by the cisternal injection of kaolin, which produces a granulomatous leptomeningitis that occludes the lateral apertures.¹¹⁶⁻¹²² In these experiments, communications were found between the dilated central canal and the syrinx in the dorsal funiculi.

Syringomyelia is classically described in two forms: Primary syrinx formation is the result of a developmental defect. Secondary syringomyelia follows a variety of primary causes: injury, vascular compromise, inflammations, neoplasia. The syrinx often results from the accumulation of edema related to the primary cause.¹²³ The ventral aspect of the dorsal funiculi has a predilection for this edema or the expansion of hemorrhagic lesions. Although a hydrodynamic explanation seems most plausible for the syringomyelia that accompanies hydrocephalus, it could be a separate developmental lesion of myelodysplasia unrelated to increased intraventricular pressure. In humans, these are referred to as dysraphic lesions because of their median plane location.¹²⁴

These spinal cord lesions can compromise the cervical spinal cord parenchyma enough to cause progressive spastic tetraparesis and ataxia. These progressive signs would support the hydrodynamic pathogenetic theory. In addition, because these lesions occur in the young growing dog and are fairly diffuse in the cervical spinal cord, a progressive cervical scoliosis may accompany the gait deficit.¹²⁵ This is also a complication of hydrocephalus and hydromyelia in

children.^{114,126} In these children, the hydrocephalus has often spontaneously arrested, but the compensatory hydrosyringomyelia is progressive, causing a progressive gait deficit and scoliosis. Surgical ventricular shunting procedures have improved these patients. These defects are seen sporadically in other species.¹²⁷

We have observed two dogs that developed progressive cervical spinal cord signs at 3.5 and 4 years of age associated with extensive cervical hydrosyringomyelia in the dorsal funiculi and bilaterally in the gray matter with no dilation of the ventricular system. Autopsy of one revealed other evidence of a myelodysplasia and no indication of another primary cause. A similar delayed clinical onset of a syringomyelia occurs in humans that may reflect decompensation due to altered CSF hydrodynamics.¹²⁸

Miscellaneous

We studied a 4.5-month-old female Dalmatian with signs of episodic cerebral disturbance (depression, dementia, propulsive circling) associated with dehydration, adipsia, and hypernatremia.¹²⁹ Clinical laboratory studies indicated defective function of osmoreceptors or thirst response and defective secretion of antidiuretic hormone. At autopsy, there was an unusual malformation of midline prosencephalic structures at the junction of the rostral hypothalamus with the cerebrum. The ventral aspect of the longitudinal cerebral fissure between the frontoparietal lobes was obliterated by the median plane fusion of the adjacent prean gyri and the ventral aspects of the caudate nuclei. This area of fusion blended caudally with the rostral hypothalamus. The corpus callosum was extremely thin. There was complete absence of the columns and body of the fornix, septal nuclei, and septum pellucidum. The rostral hypothalamus is the site of the osmoreceptors and neurons that produce antidiuretic hormone. It was assumed that their dysfunction was related to this malformation.

BRAIN STEM

Diencephalon

Microphthalmia, anophthalmia, optic nerve hypoplasia, aplasia

The eye initially develops as an outgrowth of the neural tube at the level of the prosencephalon. The neuroepithelium of this outgrowth—optic pit, vesicle, cup—forms the retina. Its optic stalk serves as a pathway for the processes of the ganglion cell layer of the retina to grow caudally to the diencephalon, forming the optic nerves, chiasm, and optic tracts. Inadequate development of this optic cup results in varying degrees of **microphthalmia** and **optic nerve hypoplasia**. This is a fairly common malformation that occurs sporadically and often is associated with other brain malformations. Complete absence of any evidence of eyeball tissue is **anophthalmia** and represents failure of optic vesicle-cup development. This is rare. Microphthalmia and optic nerve hypoplasia have been observed as the sole mal-

formation in a litter of **kittens** born from a queen treated with griseofulvin during gestation.⁴ It also occurs with the inherited craniofacial malformation of **Burmese cats**.²⁵ Optic nerve hypoplasia has been observed in **kittens**, **puppies**, and **foals** with normal-size eyeballs.¹³⁰⁻¹³² These animals are blind with widely dilated pupils unresponsive to light stimulus. There are reports of an increased incidence in **Miniature Poodles**.¹³¹ It is not known whether this is a true developmental hypoplasia or optic nerve atrophy from an abiotrophy of the retinal ganglion cells.

Normally, the majority of the optic nerve axons cross to the opposite side of the diencephalon in the optic chiasm. The percentage of crossing axons varies with the breed of animal. We have observed a family of **Belgian Sheep dogs**, with a congenital rapid pendular nystagmus, that had complete failure of the optic chiasm to develop. Each optic nerve was continued by the ipsilateral optic tract. These dogs showed no obvious signs of visual deficit. An inherited cause was assumed but not proven.

Mesencephalon

The primary malformation that results in extensive dilation of the lateral ventricles (hydrocephalus) is most often a failure of normal development of the mesencephalic aqueduct (aqueductal stenosis). (See the previous section about hydrocephalus in this chapter.) In small animals this is often associated with malformation of the rostral tectum and the formation of a single midline rostral colliculus. Abnormal angulation of the mesencephalon occurs in Hereford calves with aqueductal stenosis and other brain, ocular, and muscle abnormalities that comprise an inherited syndrome.⁸⁹

Pons

In those conditions in which the cerebrum or cerebellum fails to develop normally, there is an associated failure of development of the transverse fibers of the pons and middle cerebellar peduncles. Normally these pontine neurons are the connecting link in the cerebropontocerebellar pathway. Their normal development is dependent on their afferent and efferent connections.

Medulla

We have observed a unique **medullary dysplasia** of unknown cause that occurs sporadically in **calves** and occasionally **lambs** of different breeds and that usually presents with remarkable signs of cerebellar dysfunction from birth (Fig. 2-10). The fourth ventricle is obliterated by a transverse band of parenchyma just caudal to the cerebellar peduncles. The small remaining caudal portion of the fourth ventricle has an associated choroid plexus in its roof plate. An ependymal cell-lined duct, similar to a central canal, is continuous through this band of parenchyma connecting the two parts of the fourth ventricle. Usually a pair of cranial nerves attach to the dorsal surface of this transverse band, each associated with a small swelling. These may represent

the vestibulocochlear (VIII) nerves and cochlear nuclei, respectively. In most of these calves, there is a specific **cerebellar malformation** in which it is underdeveloped and appears to have developed in a nearly vertical plane, with the cerebellar medulla facing caudally rather than developing in a semicircle with the cerebellar medulla enclosed and facing the fourth ventricle through a narrow space between the lobules of the rostral and caudal portions of the vermis. The transversely oriented cerebellum is about 1 cm thick with the cortex in rudimentary folia on the rostral side and the white matter (medulla) on the caudal surface. The central vermal portion is the thinnest and sometimes is absent.

Various cerebral malformations have accompanied this consistent medullary malformation. These include aplasia of the corpus callosum, dilation of the lateral ventricles, the presence of clumps of ectopic cerebral cortex on the inside (ventricular) surface of the distended neopallium, and partial hydranencephaly (focal areas of cerebrum consisting only of a pial-glial membrane between lateral ventricle and subarachnoid space). A similar malformation has been reported in calves as the **Dandy-Walker syndrome**.^{133,134} The cause of this bovine abnormality is unknown. We have observed a similar medullary malformation in two lambs. One was associated with a caudal vermal cerebellar abnormality and the other with a nearly complete absence of the cerebellum, cerebral malformation, and occipital meningoencephalocele. In children, the Dandy-Walker malformation primarily involves failure of the cerebellar vermis to develop, but there are often other anomalies such as agenesis of the corpus callosum. The Dandy-Walker malformation in humans lacks the unique features of this bovine and ovine cerebellar and medullary dysplasia. (The Dandy-Walker syndrome is also discussed in the section about the cerebellum in this chapter.)

Arnold-Chiari malformation

The **Arnold-Chiari malformation** is a complex deformity of the caudal brain stem and cerebellum that was described in children in the late nineteenth century.¹²⁹ The different variations of this malformation now comprise four types. The classical Arnold-Chiari malformation consists of a lengthening and caudal extension of the vermis and paravermis (tonsils) of the cerebellum through the foramen magnum into the cranial cervical vertebral canal. The medulla is elongate, and its dorsal part extends caudally so that it overrides the most cranial of the cervical spinal cord segments. This forms a Z-shaped kink at the junction of the medulla and C1. The choroid plexus of the caudal part of the fourth ventricle and the herniated cerebellum form a compact mass of tissue adhered to the foramen magnum and cervical spinal cord. The cerebellum may be hypoplastic and asymmetrically flattened. Aqueductal stenosis and hydrocephalus often accompany this cerebellomedullary malformation. The occipital bones are usually malformed. In

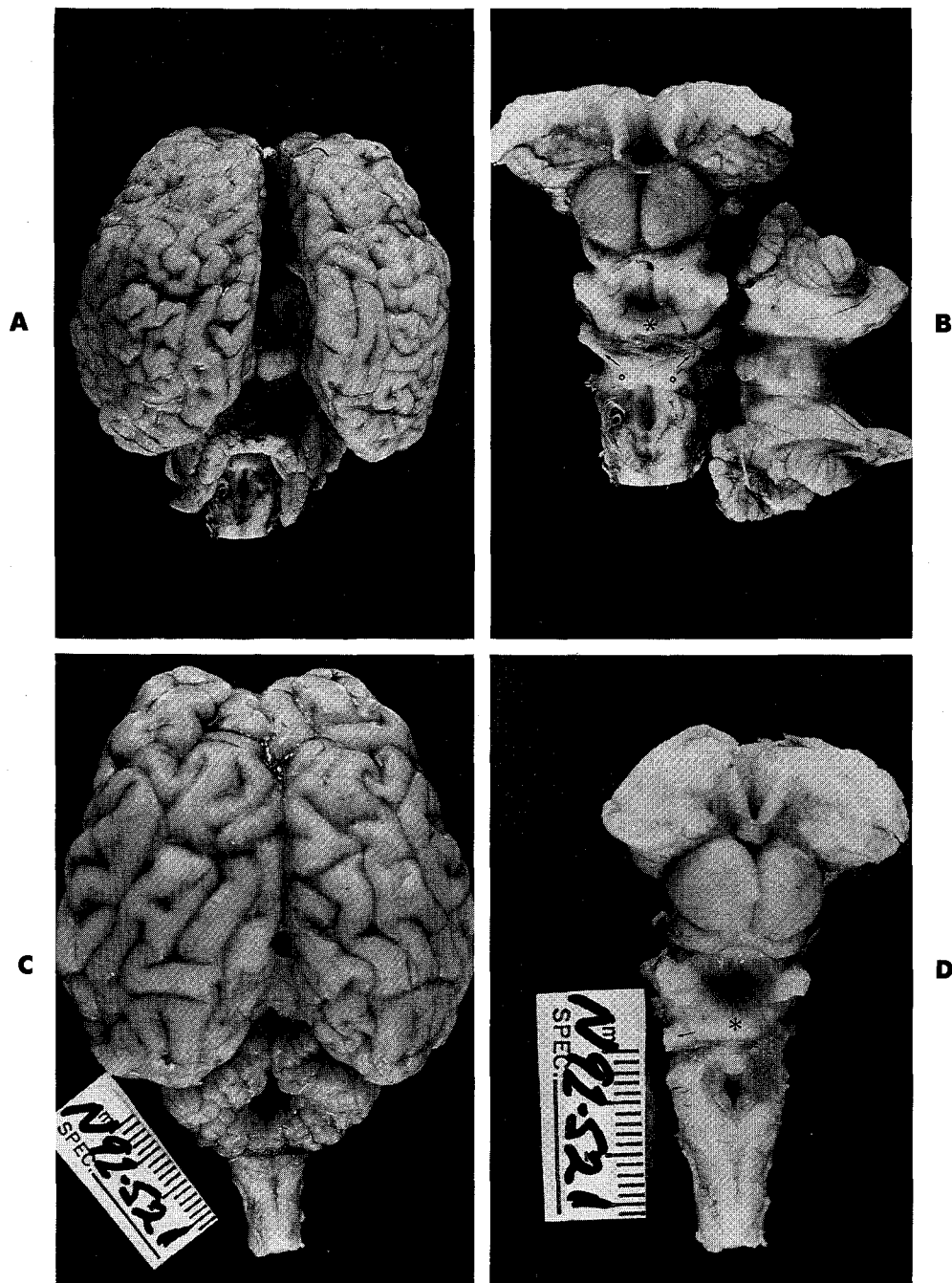


Fig. 2-10. Cerebellar and medullary malformation of calves and lambs. **A**, Calf. Cerebellar medulla faces caudally. **B**, Brain stem. Cerebellum has been removed and laid back. A transverse band of tissue (*asterisk*) crosses the fourth ventricle. Note the aberrant cranial nerves (*arrows*) and small nodules of tissue (*o*), possibly the VIII nerve and cochlear nuclei, respectively. **C**, Lamb. Vermian defect, cerebellum. **D**, Brain stem. A transverse band of tissue crosses the fourth ventricle (*asterisk*), and an aberrant cranial nerve is seen (*arrow*).

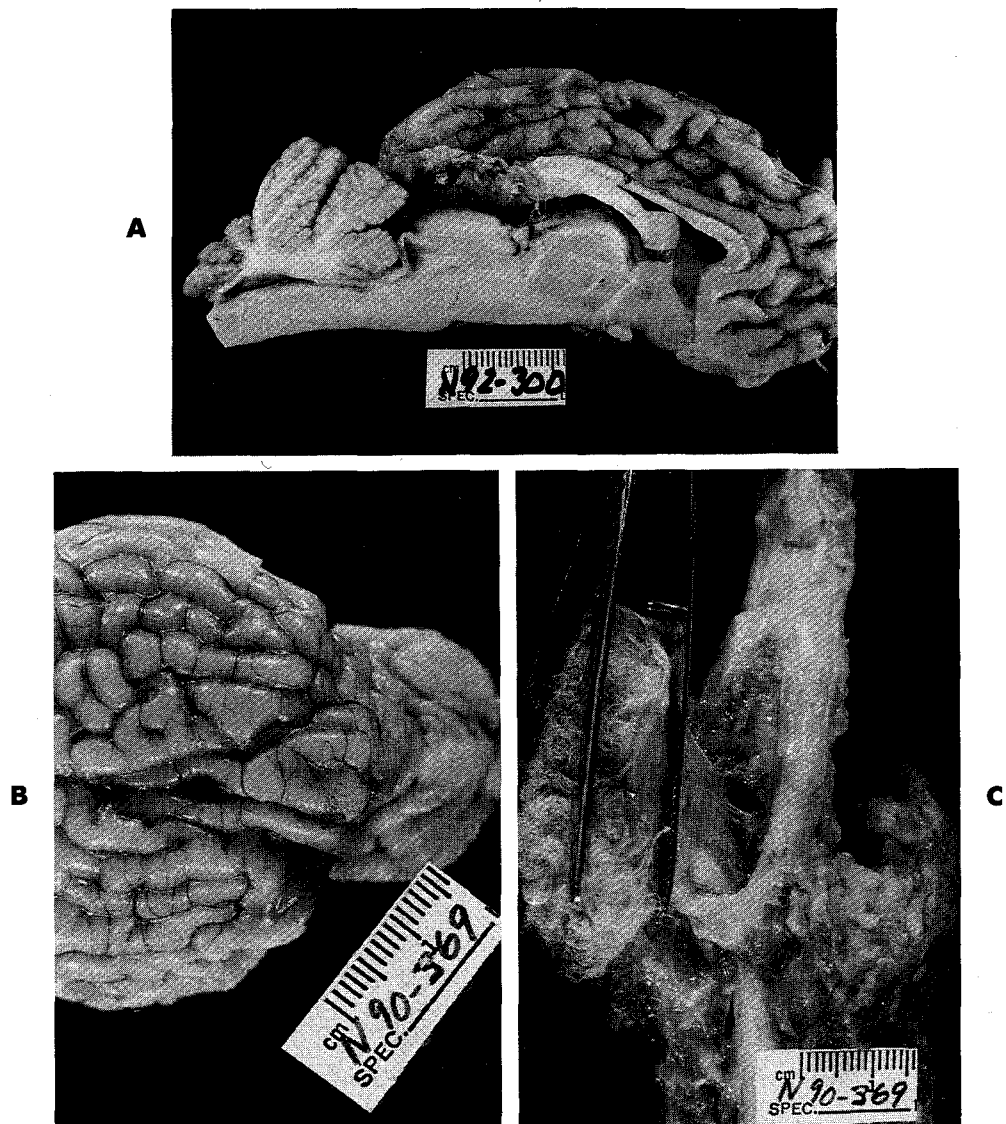


Fig. 2-11. Arnold-Chiari-like malformations. **A**, Calf. Sagittal section of brain. Elongated occipital lobe of the cerebrum and flattened brain stem. **B**, Lamb. Elongation of occipital lobe of cerebrum. **C**, Same lamb. Lumbar spina bifida and meningocele.

most of these children, there is an associated lumbosacral spina bifida, meningocele, and myelodysplasia.

The Arnold-Chiari malformation has been described in **calves** because of some features that resemble this malformation in children.^{135,136} However, there are significant differences that should be noted and that put in question the accuracy or usefulness of this comparison. The most comparable malformation is the caudal extension of the cerebellar vermis into the cranial cervical vertebral canal. Although the medulla was also described as being displaced caudally, it did not have a dorsal part that overlapped the spinal cord and created a kink at the junction between medulla and spinal cord. Although sacral spina bifida often occurred, it was rarely associated with a meningocele.

A consistent finding in these calves was a bilaterally symmetrical caudal elongation of each occipital lobe (Fig. 2-11, A). These extensions occurred caudal to an oblique groove in each cerebrum assumed to be the location of the cerebellar tentorium. The gyri of these elongations were oriented parallel to the longitudinal cerebral fissure. This cerebral malformation is not a component of the Arnold-Chiari malformation in children.

We have observed both calves and lambs (Fig. 2-11, B and C) with sacral spina bifida and meningocele, caudal extension of the cerebellar vermis through the foramen magnum and bilateral elongation and caudal extension of the occipital lobes as described for the Arnold-Chiari calves. This appears to be a specific syndrome of malformations

that occurs sporadically without a proven cause. The clinical signs usually relate to the meningocele and myelodysplasia with varying degrees of paraparesis and pelvic limb ataxia, incontinence, anal and tail paralysis, and analgesia.

A number of hypotheses have been advanced to explain the Arnold-Chiari malformation in children. One explanation for the caudal displacement of the cerebellum and medulla is that the meningocele attaches the spinal cord and/or its roots to the sacral vertebra and prevents the normal ascent of the spinal cord during growth. This caudal tethering of the spinal cord causes the caudal displacement of the cerebellum and medulla. However, the Arnold-Chiari malformation can occur without a meningocele, and there is no evidence of a caudal displacement of the thoracic spinal nerves.

CEREBELLUM

Congenital cerebellar abnormalities are common in domestic animals. The two most common causes are (1) a primary developmental defect-malformation and (2) hypoplasia and atrophy secondary to an in utero or perinatal viral infection. The latter most commonly occurs in cats and cattle but has also been described in sheep, pigs, and dogs.

Viral infections

Cat. A congenital cerebellar abnormality has been recognized in cats since at least 1888;¹³⁷ it is associated with clinical signs of severe cerebellar ataxia (basewide stance, spastic-hypermetric gait, loss of balance) from the time the affected kitten is able to stand and walk. It was not until 1965 that its relationship with a viral infection was established.¹³⁸ In 1967, this was identified as the **feline panleukopenia virus** (parvovirus).¹³⁹ The exact time of CNS infection, whether occurring in utero or postnatally, is unknown, although transplacental infection is favored.¹⁴⁰ However, the cerebellum continues to develop in the postnatal period and infection at birth would result in significant hypoplasia. The cell population most susceptible to this viral infection is the external germinal layer of the cerebellum that is most actively proliferating at the time of birth and for the first 2 weeks postnatally. The virus has a predilection for actively dividing cells and destroys this layer, presumably in the perinatal period. This causes hypoplasia of the granule layer and disorganization of the Purkinje cells in the folia. The virus or the resulting inflammation also destroys already differentiated Purkinje neurons and parenchyma, often resulting in remarkable atrophy of the cerebellum.

At the time of autopsy, weeks to months after birth, the pathologist is left with the cerebellar remains to study (Fig. 2-12). The gross cerebellar lesion varies from subtle overall reduction in size with a slight narrowing of the folia to an extensive loss of cerebellar tissue with little evidence of folial development. When the cerebellar lesion is extensive,



Fig. 2-12. Panleukopenia virus-induced cerebellar hypoplasia, cat. **A**, Intact small cerebellum. **B**, Transverse sections through cerebellum and medulla.

there is an associated decrease in size of the transverse fibers of the pons and pontine nuclei. Beware that in the newborn kitten and puppy the cerebellum is normally very small; this should not be confused with cerebellar hypoplasia and atrophy.

In the dog and cat, cerebellar development continues postnatally for up to 10 weeks through the differentiation of the external germinal layer. Remnants of this layer can persist for months in all species and should not be confused with an inflammatory lesion. On microscopic examination of the abnormal cerebellum, no inflammation is observed and the lesion varies from just a loss of granule cells and disorganized Purkinje neurons (granuloprival hypoplasia) (Fig. 2-13) to rudimentary folia completely lacking in neuronal cell bodies.^{141,142}

Evidence that the virus occasionally affects other neuronal populations includes the rare observations of hydranencephaly or of hydrocephalus secondary to aqueductal stenosis in newborn kittens with cerebellar lesions. Occasionally, kittens that have the characteristic cerebellar lesion also have bilateral plaques of mineralization in the cerebral in-

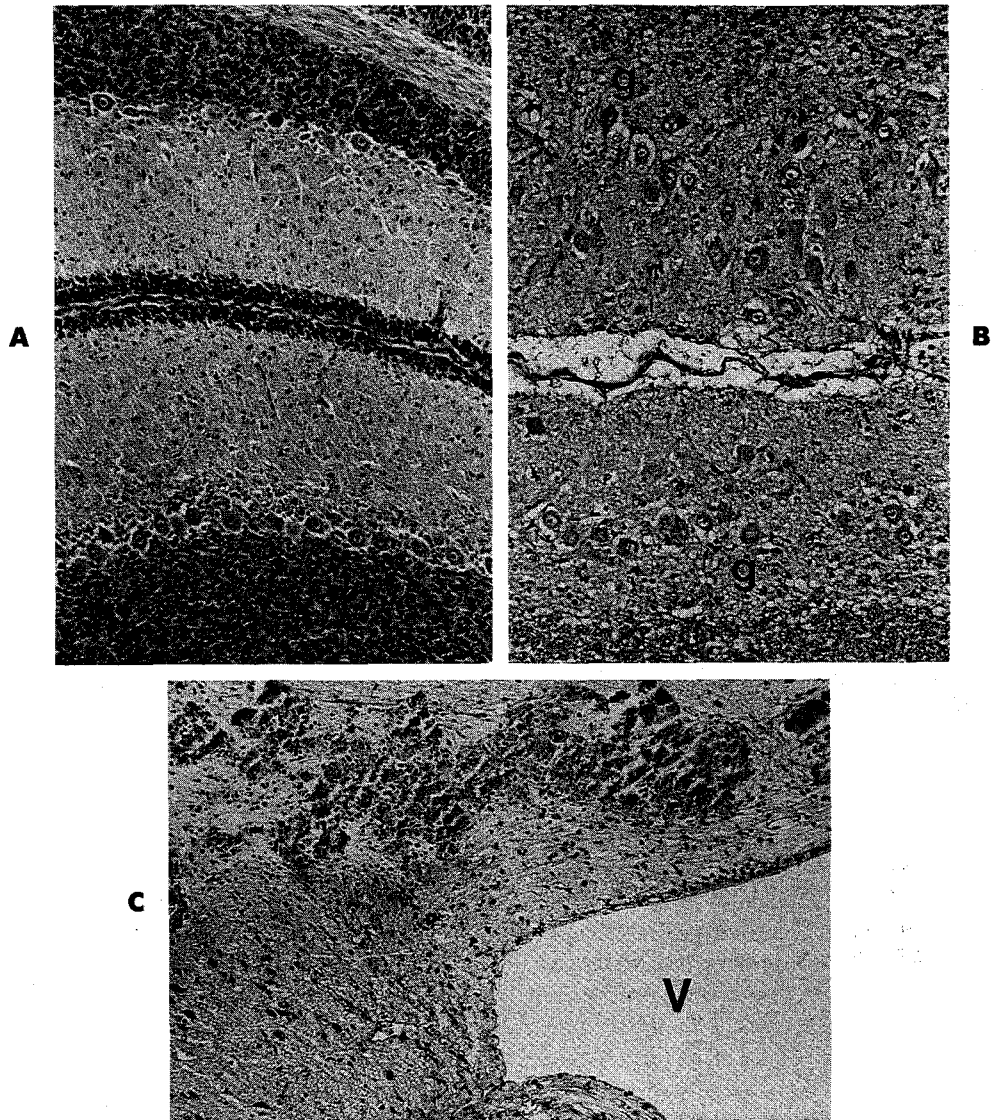


Fig. 2-13. Panleukopenia virus-induced cerebellar hypoplasia, cat. **A**, Normal cerebellar cortex, young kitten. (H&E, $\times 140$.) **B**, Viral injury depletes the external germinal layer. There is heterotopia of Purkinje cells within the narrowed molecular layer. Granule cell layer (*g*) is severely depleted. (H&E, $\times 140$.) **C**, An occasional finding is periventricular necrosis and mineralization; lateral ventricle (*v*). (H&E, $\times 140$.)

ternal capsules or periventricular tissues (Fig. 2-13, C). These are presumed to result from viral-induced necrosis and subsequent mineralization.

Cattle. In 1968, the first relationship was made between newborn calves with cerebellar abnormalities and infection of pregnant dams with the **bovine virus diarrhea (BVD)** agent (genus *Pestivirus*).¹⁴³ This was further supported by recognizing antibodies to BVD in the serum of affected calves prior to their ingestion of colostrum.^{144,145} The lesion was experimentally produced in calves by exposing susceptible pregnant dams to the BVD virus between 100 and 200 days of gestation.¹⁴⁶ The acute inflammatory lesion in the cerebellum caused by this agent was studied in bovine

fetuses examined 17 to 21 days after the exposure of dams to the agent at 150 days of gestation.^{147,148} This consisted of an extensive nonsuppurative inflammation, predominantly in the cerebellar cortex and adjacent leptomeninges with widespread necrosis of neuronal elements and neuropil with hemorrhages and severe edema of the folial and medullary white matter.

This cerebellar lesion causes varying degrees of neurological signs. Many calves are severely affected clinically and are unable to stand. They remain bright and alert and eat well. They can kick and thrash with their limbs vigorously but cannot coordinate these actions to stand. Head movements also cannot be coordinated, and the calf may

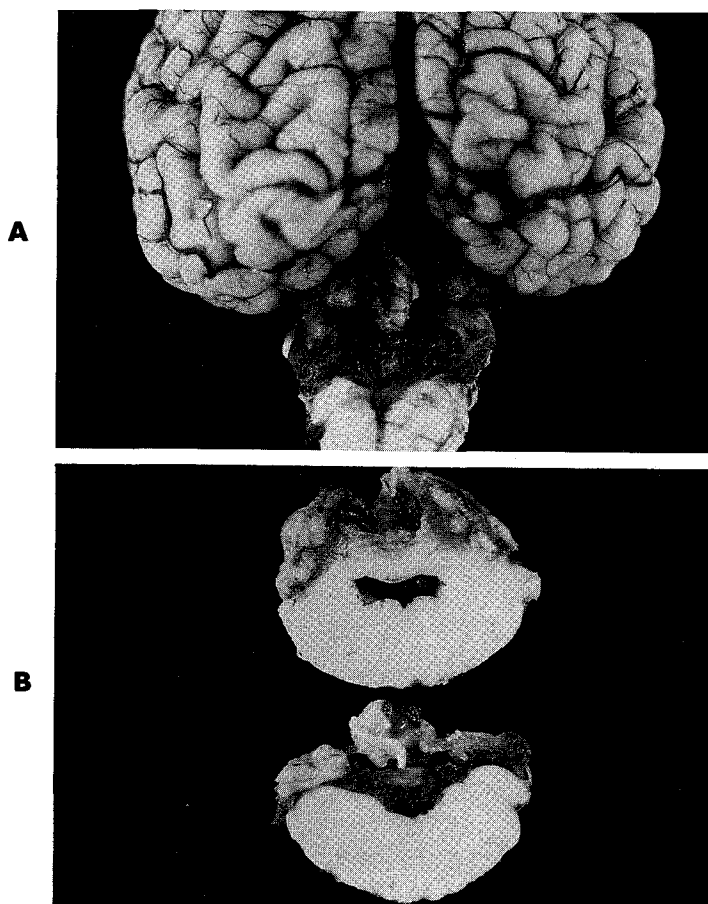


Fig. 2-14. BVD virus-induced cerebellar hypoplasia-atrophy, calf. **A**, Remnants of cerebellum. **B**, Transverse sections through cerebellum and medulla.

sway and lurch in all directions. Occasionally the head extends caudally in an opisthotonic posture. Calves that can stand typically have a basewide posture, sway in all directions, and walk with a jerky spastic dysmetric-hypermetric gait, frequently stumbling or falling in any direction from loss of balance. Head tremor and abnormal nystagmus are uncommon. Vision is normal if ocular lesions are mild. With severe retinal or optic nerve lesions, the calf is blind, with dilated pupils unresponsive to a light stimulus.

At autopsy of the newborn calf, varying degrees of gross cerebellar abnormality are observed. Usually the loss of cerebellar tissue is symmetrical and fairly extensive. In many calves, only a small remnant of parenchyma remains, spanning the fourth ventricle (Fig. 2-14). This band of tissue usually has a few remnants of folia on it. Occasionally fluid-filled cavities (cysts) occur in the folia. The meninges are collapsed on this cerebellar remnant. Before death, these meninges lined the walls of the fairly normal-size caudal fossa, and CSF filled the space where the cerebellar tissue was lost. The transverse fibers of the pons are usually small, and their degree of diminution varies directly with the degree

of cerebellar atrophy. Microscopic examination reveals the end result of the inflammation that occurred in utero. No inflammation remains at birth. The remaining folia vary from normal to having a complete loss of cerebellar cortex. Some folia may remain only as narrow extensions of pial-covered neuropil. Some folia show single to multiple foci of cortical atrophy or dysplasia. Normal and severely atrophic cortex can occur on opposite sides of a folium. Some folia have large cavities in their white matter. The cortex lining these cavities varies from normal to completely atrophic. Usually these lesions are limited to the cerebellum. In a few calves, porencephalic lesions also occur in the cerebrum, especially in the occipital lobes, where they may be associated with dilation of the adjacent lateral ventricle. These cavities are lined by astrocytes and usually communicate with the lateral ventricle. When extensive, they may extend through the adjacent gray matter, producing a focal area of hydranencephaly. Rarely, hydranencephaly and porencephaly with microencephaly have been observed in calves with extensive cerebellar lesions related to a BVD virus infection.¹⁴⁹ Ocular lesions commonly occur and include retinal atrophy and dysplasia, optic neuritis and atrophy (Fig. 2-15, A), microphthalmia, and cataracts.¹⁵⁰

Some fetal infections with the BVD agent are associated with modest to extensive **hypomyelination** throughout the CNS (Fig. 2-15, B).^{151,152} At birth, these calves have a severe, whole-body, rapid tremor associated with any voluntary muscle activity. The tremor disappears when they are recumbent and totally relaxed. Sometimes they cannot stand. Others walk with varying degrees of ataxia, but usually it is mild and masked by the severe tremor. Some calves spontaneously improve in a few days to weeks, presumably as their myelination occurs.

The outcome of BVD virus infection of the bovine fetus is determined by host (developmental stage of the target tissue, immune competence) and virus (strain) factors.^{153,154} The classical lesions of cerebellar necrosis and cavitation may result from the inflammatory response to the agent.

Cerebellar lesions may also occur in bovine fetuses infected with the **Akabane**, **Bluetongue**, or **Wesselsbron** viruses. However, they are usually less extensive than the cerebral lesions of hydranencephaly or porencephaly. The same occurs in lambs with Akabane or Bluetongue infection.

Fig. Hog cholera vaccine virus administered to susceptible pregnant sows and natural infections can result in fetal pig lesions, including cerebellar degeneration-hypoplasia, microencephaly, and hypomyelination.¹⁵⁵⁻¹⁵⁷ At birth, these pigs have a diffuse whole-body tremor and cerebellar ataxia. Similar clinical signs and lesions have been observed in pigs born from sows that were treated for parasites with trichlorfon (Neguvon, an organophosphate) during gestation.^{158,159}

Dog. In dogs, no viral agent has been implicated in causing in utero infection of the brain or inflammation restricted to the cerebellum in the neonate. The canine **herpes virus**

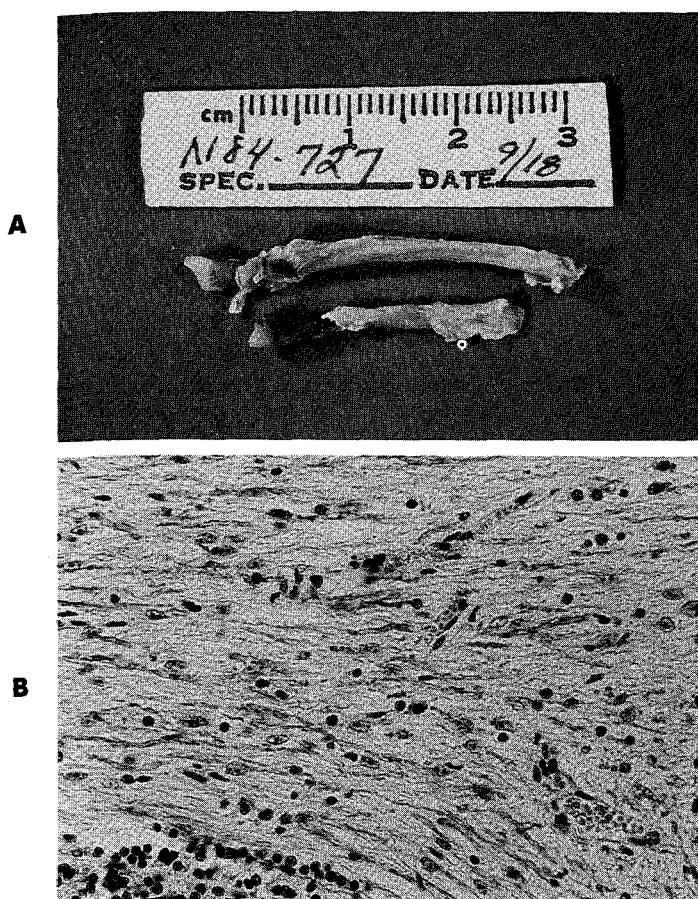


Fig. 2-15. Effects of BVD virus in utero. **A,** Bilateral optic nerve atrophy. **B,** Hypomyelination (cerebellum). (Myelin stain, $\times 350$.)

causes extensive inflammation in multiple systems of newborn puppies. This includes an acute encephalitis. If a puppy survives the infection, it may have a cerebellar ataxia from the residual effects of the inflammation that involved the cerebellum.¹⁶⁰ We have observed a young adult Beagle dog with unknown history that had static signs of a severe cerebellar disorder. At autopsy, the moderately atrophic cerebellum had extensive microscopic lesions typical of those seen in cats and cattle following their in utero viral infections. The cause of the presumed inflammatory lesion in this dog is unknown.

Horse. No in utero viral infections of the equine fetal nervous system have been recognized. The Arabian foal that has progressive cerebellar ataxia at birth has an abiotrophy of cerebellar cortical neurons that is presumed to be inherited. Usually the signs do not occur until a few weeks postnatally.

Primary malformations

Cattle. A sporadic primary cerebellar malformation in newborn calves was previously described with the unique

brain stem–medullary dysplasia that has been reported as the Dandy-Walker malformation. In this syndrome, the cerebellum develops as a narrow, transversely oriented structure with small folia primarily on its rostral surface and the medullary white matter exposed caudally. This has the appearance of a cerebellum that failed to develop its normal rostrocaudal curvature that encloses the cerebellar medulla between the rostral and caudal lobules of the vermis. The clinical signs primarily reflect the cerebellar abnormality. The cause is unknown.

We have had the occasional experience of performing an autopsy on a young calf that had signs since birth of severe cerebellar ataxia, identical to calves with the typical cerebellar lesion caused by the BVD agent, and found no gross or microscopic lesions in the entire central nervous system. We propose that these calves may have a neurochemical abnormality responsible for the cerebellar signs but without recognizable structural abnormality. In these situations, it is tempting for the inexperienced to describe normal microscopic features as abnormalities. These normal features that can be confused for lesions include the persistence of the external germinal layer as a single layer of cells for a variable number of months postnatally, the presence of normal small gaps in the Purkinje neuron layer where Purkinje neurons are absent, and the recognition of large pyramidal neurons in the granule neuron layer and occasionally in the folial white matter. These latter neurons are not misplaced cells. These can be found normally in all domestic animal cerebellums. Although they look like Purkinje neurons, immunocytochemistry suggests they are Golgi neurons. Fixation artifacts can be extensive in the cerebellar cortex and especially in the Purkinje neuron layer. Dark red Purkinje neurons, peripheral vacuoles in the cytoplasm of Purkinje neurons, and vacuolated neuropil in the Purkinje neuron layer are common artifacts. In the bovine cerebellum, autolysis may cause extensive pyknosis and neuropil vacuolation in the granule layer.

Cerebellar hypoplasia and dysplasia with extensive disorganization of the cerebellar cortical layers occur in **Hereford calves** as one of a group of specific brain anomalies. This was described as an example of polymicrogyria. Clinical signs reflect a diffuse neurological disturbance.⁸⁹ Cerebellar hypoplasia has been reported in **Shorthorn** and **Angus calves** as an autosomal recessive disorder.¹⁶¹⁻¹⁶³

Dog. Primary cerebellar malformations produced congenital signs of severe cerebellar ataxia in multiple members of a litter of **Wire Fox Terriers** and a litter of **Irish Setters**. All affected dogs also had lissencephaly, which was more extensive in the Wire Fox Terriers. The cerebellar lesion in the Wire Fox Terriers consisted of a marked symmetrical hypoplasia with dysplasia of the cortical elements in the rudimentary folia. In the Irish Setters, the hypoplastic cerebellum developed as a transversely oriented, narrow vertical structure with rudimentary folia projecting from it. Although a genetic basis for these was proposed, no further

examples have been seen in either breed.

Cerebellar cortical abiotrophy usually presents as a postnatal progressive disorder and is described under degenerations of the nervous system. An abiotrophy is a degeneration due to an intrinsic developmental abnormality of the cell causing its premature death. Occasionally, this lesion and the clinical signs it produces have been seen at birth in dogs, cattle, and sheep. Microscopically, there is a loss of Purkinje neurons and evidence of Purkinje neuron degeneration. Granule neuron reduction is thought to be secondary to the loss of their target neuron, the Purkinje neuron. A recessive inheritance has been suspected when enough affected animals have been observed. The breeds involved include Beagle and Samoyed dogs, Hereford cattle, and Welsh Mountain and Corriedale sheep. The affected sheep are referred to as daft lambs.¹⁶⁴⁻¹⁶⁶

Horse. Cerebellar hypoplasia or aplasia and other brain malformations were observed in two equine fetuses aborted at 8 months because of hydrops allantois.¹⁶⁷ The other anomalies were cerebral hypoplasia, hydrocephalus, and hydranencephaly.

Dandy-Walker syndrome

Cerebellar malformations occur in domestic animals in which the only or primary lesion is a partial or complete absence of the vermis of the cerebellum. Reports are most common in **calves** and **dogs**^{133,134,168-171} but include the **foal**,¹⁷² and we have observed it in a **lamb**. Most show signs of cerebellar ataxia similar to those seen with other cerebellar lesions. These vermal defects are often referred to as examples of the **Dandy-Walker syndrome**.¹⁷² This is a syndrome described in children whose primary abnormality is partial or complete absence of the cerebellar vermis.¹²⁸ Partial agenesis always involves the caudal aspect of the vermis. Associated with all these vermal defects is cystlike dilation of the fourth ventricle. In addition, many of these patients have dilated third and lateral ventricles (hydrocephalus), stenosis of the aqueduct, and absence of the corpus callosum. Some patients have cerebral and cerebellar heterotopias, polymicrogyria, microencephaly, occipital meningocele, and syringomyelia.^{173,174} Originally, the cerebellar lesion was thought to result from abnormal development of the apertures of the fourth ventricle necessary for intraventricular CSF to circulate to the subarachnoid space. Now this malformation is considered to be a primary parenchymal midline developmental field defect of unknown origin.¹⁷⁵ Calves with this cerebellar malformation also have agenesis of the corpus callosum and significant, novel, brain stem medullary abnormalities.^{133,134} The latter medullary malformation is described with the medulla and is unique in its consistent appearance. It has not been reported in the human syndrome.

We have observed one lamb with a similar cerebellar vermal defect, agenesis of the corpus callosum, and the same medullary malformation. Another lamb had the same medullary malformation with nearly complete absence of

the cerebellum, polymicrogyria of the cerebrum with heterotopic neocortex, and occipital meningoencephalocele. The last consisted of an extension of apparent leptomeninges from the dorsal surface of the pontomedullary junction through a 1.5-cm oval cranium bifidum to a protruding patch of skin that lacked hair development. The inner surface of this protruding meningeal tissue was lined with choroid plexus, indicating the presence of neuroepithelium and therefore a meningoencephalocele.

Spinal cord

In our experience, spinal cord malformations are more common in calves than in smaller ruminants.¹⁷⁶ However, they are all sporadic and of unknown etiology. Inherited and sporadic forms occur in dogs and cats.

Meningocele, meningomyelocele

Most **meningoceles** and **meningomyeloceles** involve the sacrocaudal roots and spinal nerves with a sacral or occasionally caudal lumbar spina bifida. Varying degrees of myelodysplasia of sacrocaudal and occasionally caudal lumbar segments often accompany the meningomyelocele. Although this term suggests the presence of a swelling (*-cele*) of meninges and concomitant involvement of the spinal cord segments (*myelo-*), more often there is no meningeal cyst, only a direct, tubelike extension of the meninges with their subarachnoid space through the vertebral defect to attach to the overlying skin. This meningeal extension is accompanied by intradural and extradural roots that terminate in the same region of the skin. It is unusual for the spinal cord segments to be directly involved in the meningocele.

The most common clinical signs are incontinence and loss of sensory and motor innervation of the tail, anus, perineum, and excretory organs. With significant myelodysplasia, a gait defect may be observed. Occasionally, these meningomyeloceles are associated with brain malformations that include a caudal extension of the cerebellar vermis and bilateral caudal extension of the occipital lobes. This has been compared to the Arnold-Chiari malformation in children, but significant differences exist.

Occasionally these malformations occur in the thoracic or cranial lumbar area. We observed in a newborn calf a midline pedunculated mass of skin over the sixth thoracic spine associated with spina bifida of this vertebra and a meningocele that included a dermoid cyst in the base of the meningocele at the spinal cord. These meningoceles occasionally include a large accumulation of adipose tissue in the area of involved skin—a **lipomeningocele**.

Diplomyelia, diastematomyelia

Spinal cord duplication has been observed in **calves**, most commonly in the lumbar and sacral segments. It occurs

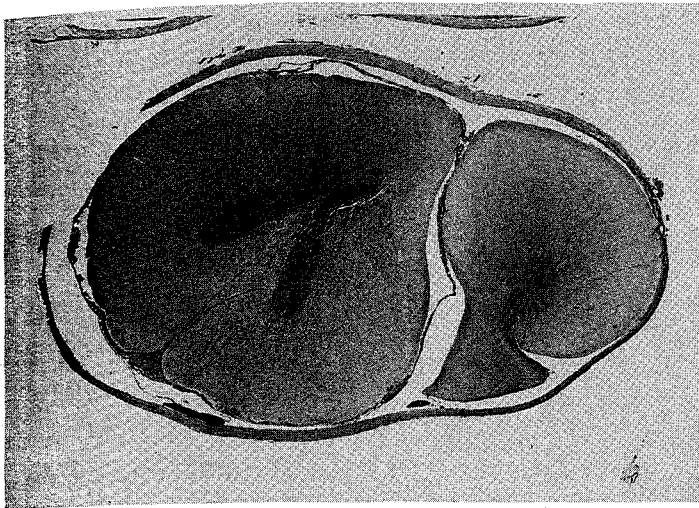


Fig. 2-16. Diplomyelia, calf. Note the common dural sheath enclosing partially duplicated spinal cord.

in two forms that probably result from an underlying notochordal abnormality. The initial induction of neuroectoderm of the neural plate is dependent on notochordal interaction. One form of spinal cord duplication occurs within a common covering of leptomeninges and dura. This is **diplomyelia**. The degree of duplication is variable and often incomplete, especially on the median plane and often with asymmetrical gray matter development (Fig. 2-16). Aberrant extraspinal rootlets are often associated with the redundant spinal cord tissue. Mechanisms that give rise to diplomyelia vary with the region of the spinal cord.¹⁷⁷ The cervical and thoracic portions of the neural tube form by the classical folding of the neural plate. Abnormal dorsal folding could result in the formation of two adjacent neural tubes. Normally the lateral edges of the neural plate progress dorsomedially to meet and fuse on the median plane, closing the neural tube. If the two approaching edges of the folds do not fuse but turn ventrally and continue to grow ventrally adjacent to each other, they will meet and fuse with the neuroectoderm of the plate ventrally. This will produce two adjacent neural tubes enclosed in a single covering of meninges. In the lumbosacral area that develops caudal to the caudal neuropore, the neural tube forms by the caudal extension of a solid cord of neuroectodermal cells from the neuroectoderm closing the caudal neuropore. This grows caudally in relationship to the regressing primitive streak and subsequently canalizes to form a neural canal. A dual origin of this proliferatory cord of neuroectodermal cells or abnormal canalization of this cord could also give rise to two adjacent neural tubes within a common covering of meninges (diplomyelia).

The second form consists of two separate spinal cords, each contained in its own meningeal covering and in separate vertebral canals. The paired vertebral canals are usually

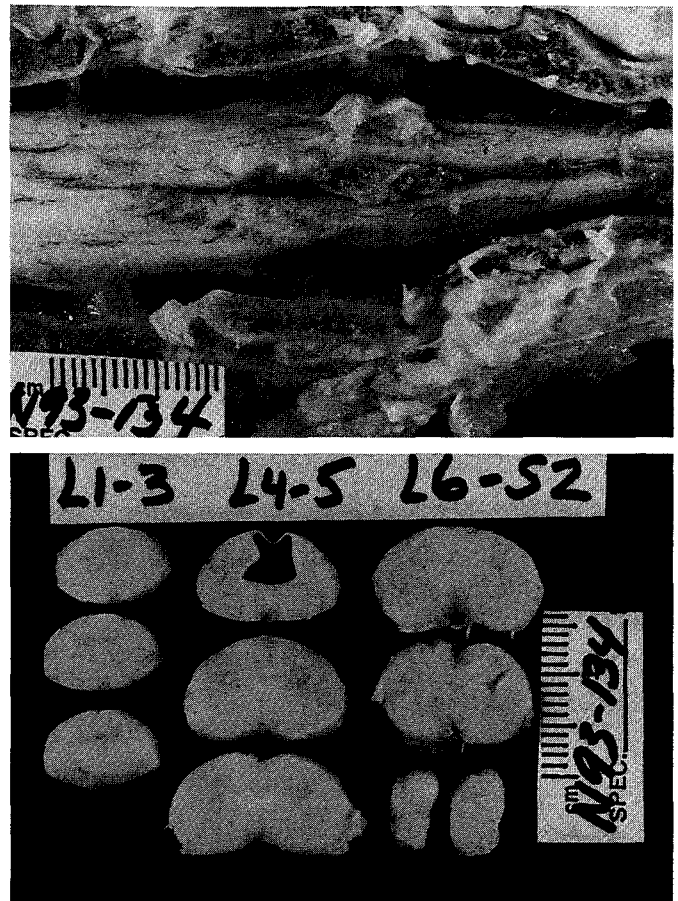


Fig. 2-17. Diplomyelia and diastematomyelia, calf. A, Note bony septum between duplicated and separated spinal cords. B, Transverse sections from L1 to S2; syrinx at L4, diplomyelia L5-S1 and diastematomyelia at S2.

associated with single but enlarged vertebral bodies with a bony partition separating the two canals. This malformation is called **diastematomyelia** (Fig. 2-17).¹⁷⁸ We observed a Hoslstein calf without a tail (acaudatus) and with a broadened lumbar vertebral column that had two completely separate lumbar and sacral spinal cords. They arose from a single normal spinal cord at T13 and joined caudally at the level of the caudal segments.

One of the most flagrant examples of a malformation specifically selected for by breeders is the caudal vertebral aplasia of the **Manx cat** (Fig. 2-18).¹⁷⁹⁻¹⁸² The extremely high incidence of sacrocaudal meningoceles, meningomyeloceles, and myelodysplasia of the caudal lumbar, sacral, and caudal segments is to be expected considering the well-known close developmental relationship of these structures. Many kittens are culled early in life because of the severe gait deficit caused by extensive myelodysplasia. Others are culled when it is recognized that they are incontinent and unaware of their excretory functions. The myelodysplasia associated with the meningomyelocele includes central canal

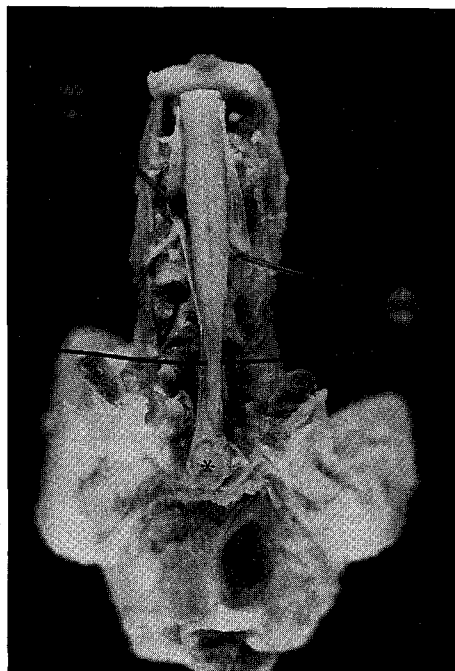


Fig. 2-18. Sacral spina bifida and meningocele, Manx kitten. Black suture passes between dura and conus medullaris. Asterisk marks attachment to skin.

defects, syringomyelia, and abnormal gray matter differentiation. These could readily be prevented by selecting for Manx cats with normally developed tails. The perpetuation of a tailless Manx cat is an unethical, inhumane breeding practice.

Similar spina bifida, meningoceles, and myelodysplasia occur sporadically in **dogs** with a presumptive inherited form in the **English bulldog**.¹⁸³ The most common clinical signs include incontinence and analgesia and muscle denervation in the tail remnant, anus, perineum, bladder, urethra, and rectum.

In children with spina bifida and meningocele, clinical neurological signs may progressively deteriorate during periods of normal growth. This is referred to as the tethered cord syndrome because of the abnormal tension exerted on the spinal cord by the meningeal attachment in the meningocele at the time of rapid growth and normal ascent of the spinal cord as the vertebral column outgrows it. Surgical severance of this attachment may provide relief from the progressive signs but not the congenital signs. A similar syndrome has been described in an English bulldog.¹⁸⁴ In children, it is also common for the meningocele to communicate with the skin and for CSF to leak through this conduit. These are closed surgically to prevent infection of the nervous system. This communication is not commonly observed in similar congenital spinal cord lesions in domestic animals.

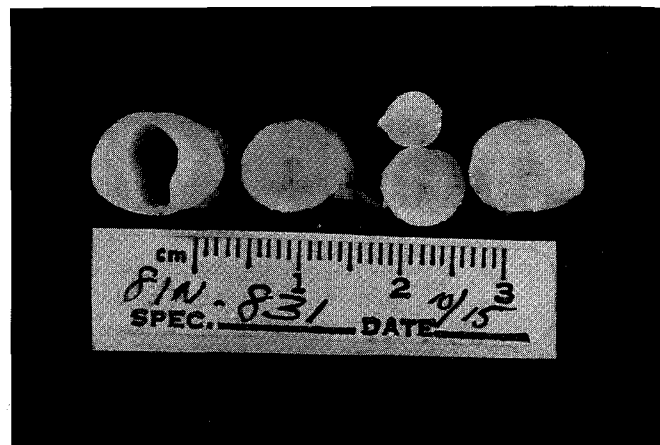
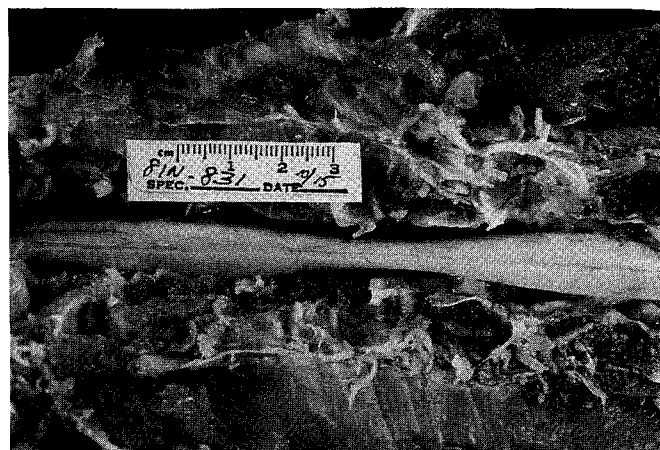


Fig. 2-19. Spinal cord hypoplasia and myelodysplasia, calf. **A**, Segmental hypoplasia, L3-L5. **B**, Transverse sections reveal a syrinx at L2 and segmental hypoplasia. The spinal cord is also dysplastic, lacking a ventral median fissure and a central canal.

Myelodysplasia

Myelodysplasia is a general term used for malformation of the spinal cord that usually includes a number of related morphological abnormalities. Segmental hypoplasia usually involves two or three adjacent spinal cord segments (Fig. 2-19). Extensive dysplasia is common within these segments and includes various combinations of hydromyelia, syringomyelia, absence or duplicated central canal, abnormal distribution-migration of gray matter into its normal columns and failure of formation of a ventral median fissure.¹⁸⁵⁻¹⁹⁰

Regardless of the nature of the thoracolumbar spinal cord malformation, the clinical signs are usually very similar. Often the affected animal cannot use its pelvic limbs to stand and walk. If supported by the tail, the forelimbs walk normally. The pelvic limbs occasionally have no voluntary movement but more often have a delay in protraction; when it occurs, both limbs move simultaneously in a bilateral hopping-like motion. This lack of alternate limb movements

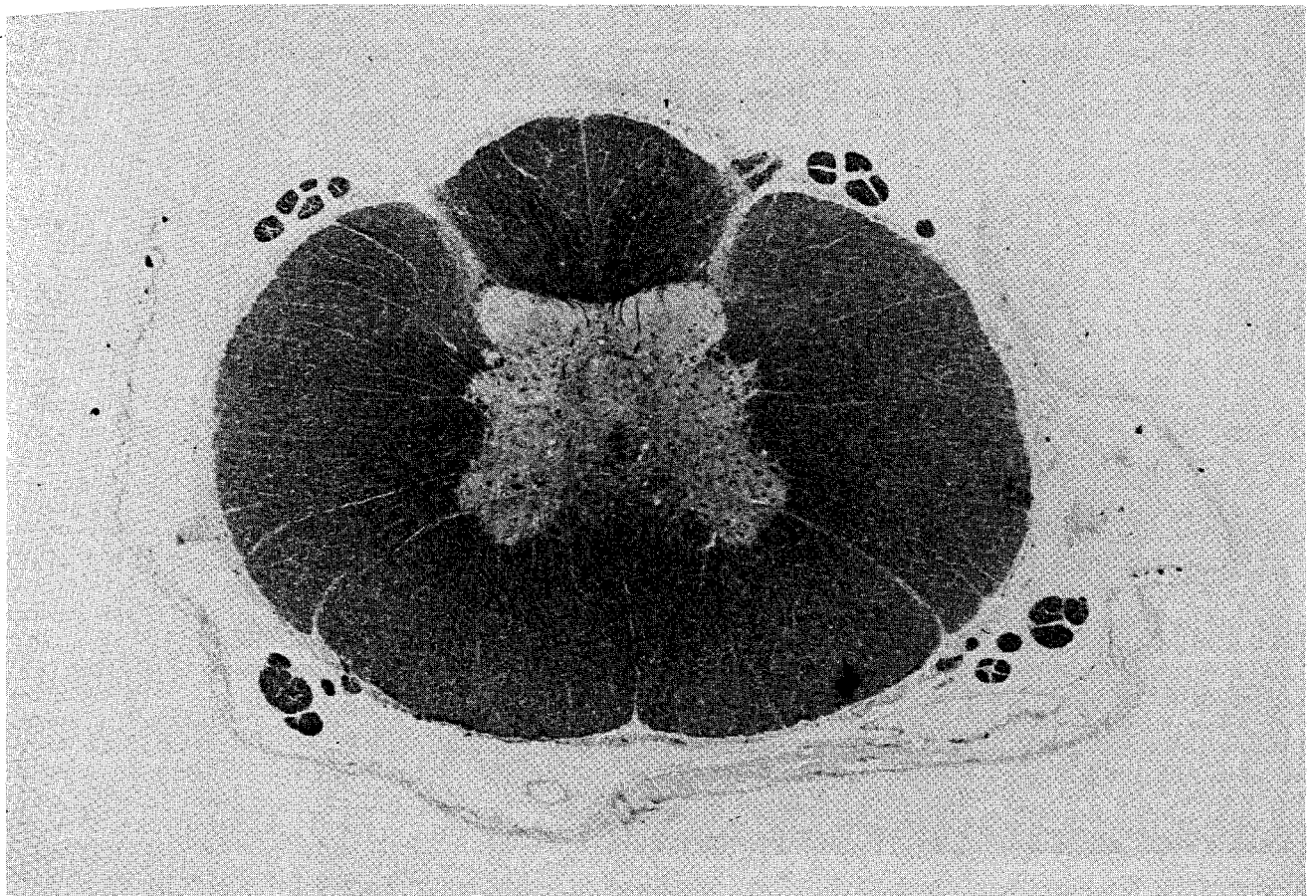


Fig. 2-20. Myelodysplasia, Weimaraner dog. Thoracic spinal cord with midline abnormalities: absence of a central canal, incomplete separation of the ventral horns, and lack of a ventral median fissure ($\times 37$).

on trying to walk is a common sign of spinal cord malformation. The animal readily sways to either side and usually needs manual support to stand. Pelvic limb tone, muscle size, and spinal reflexes are normal. Tone and reflexes may be exaggerated.

It is common for vertebral abnormalities to be associated with various forms of spinal cord malformation. This reflects the close embryonic origin of the derivatives of the spinal cord and vertebral column. Normal spinal cord and vertebral development requires precise interaction between the notochord, neural tube, and sclerotomal mesoderm. Often the vertebral abnormality is only a mild scoliosis or kyphosis.

A spinal cord malformation is inherited in **Weimaraner dogs**.¹⁹¹⁻¹⁹⁴ It has been called spinal dysraphism and compared to a similar malformation in children. This name implies an abnormality in closure of the neural tube, which is not apparent. The **thoracolumbar myelodysplasia** primarily affects midline structures with central canal abnormalities including its absence or dilation (hydromyelia), absent or forked ventral median fissure, and failure of neuronal cell bodies to migrate laterally into the ventral gray column, leaving them scattered across the dorsal aspect of

the ventral funiculi (Fig. 2-20). Syringomyelia occurs but has been described as delayed in its formation until the dogs are a few months old. Other lesions that accompany this myelodysplasia include scoliosis, abnormal dorsal cervical hair patterns, and koilosternia, a median plane depression of the sternum. It is hypothesized that this is inherited as a codominant lethal gene with variable penetrance. The homozygous condition is lethal. Clinically affected dogs are heterozygotes. The classical sign associated with this myelodysplasia is a "bunny-hopping" gait. On any attempt to move the pelvic limbs, they are simultaneously protracted. No or very little normal alternate limb gait occurs. Proprioceptive deficits may accompany this unique gait. The pathogenesis of this gait abnormality is unknown. It is rarely seen in acquired spinal cord disease and also characterizes the limb movements seen in calves with different forms of myelodysplasia. We have observed Weimaraner puppies with this characteristic abnormal gait but no microscopic spinal cord lesions. We assume that the interneuronal anatomy or activity between the ventral gray columns of the two sides of the lumbosacral intumescence is abnormal but not evident on microscopic study. Similar myelodysplasias

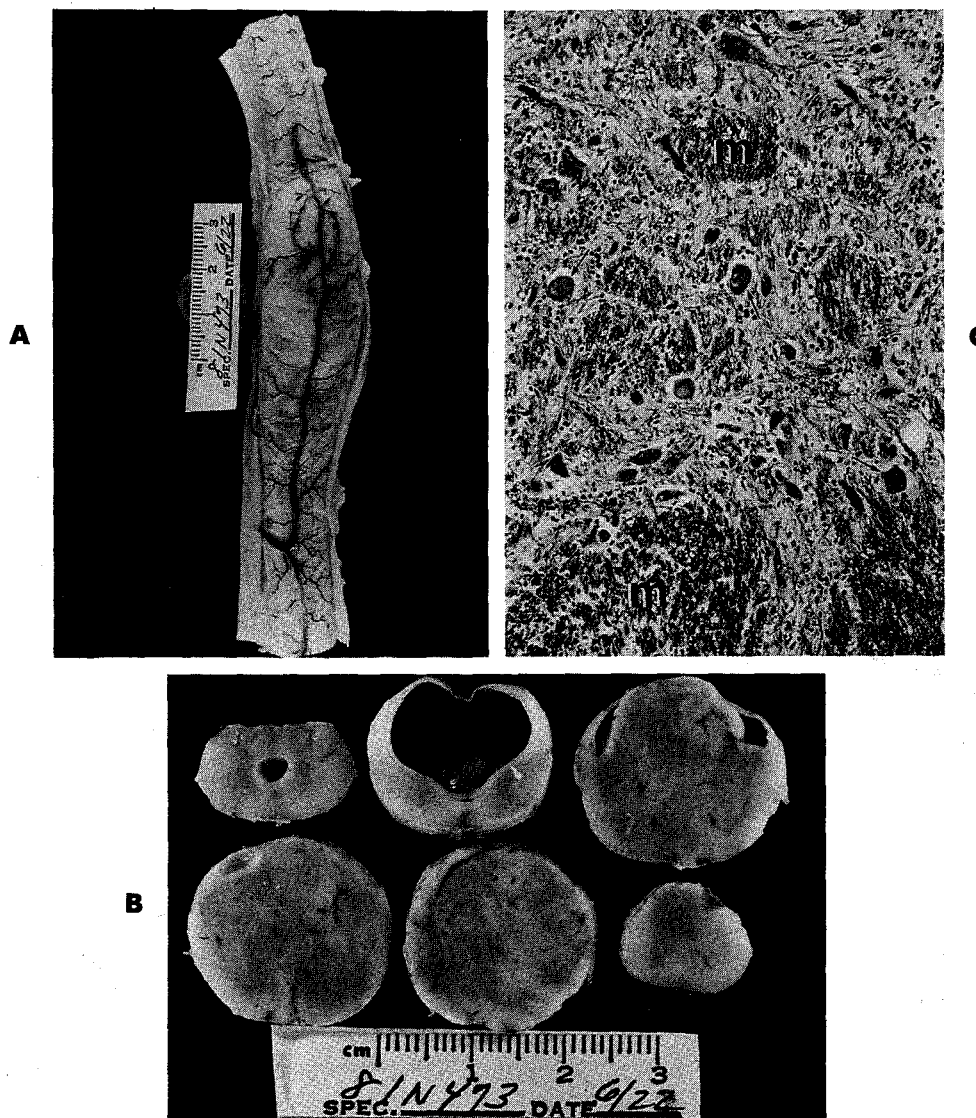


Fig. 2-21. Spinal cord hamartoma, foal. **A**, Curvature of T6-T8 spinal cord that was associated with a scoliosis. The central portion of the cord is swollen. **B**, Transverse sections from T6-T8 showing hamartomatous mass and syrinx. **C**, Histological section of the hamartoma showing haphazardly disposed neurons (*arrows*) and bundles of myelinated fibers (*m*). (Luxol fast blue, cresyl echt violet, $\times 140$.)

and clinical signs of a bunny-hopping gait have been observed sporadically in other breeds of dogs.

Myelodysplasia of the cervical spinal cord with associated clinical signs is rare in our experience. Necropsies of dogs with acquired spinal cord lesions occasionally reveal a myelodysplasia that has not caused clinical signs, such as syringomyelia, central canal abnormalities, or aberrant gray column development.

Miscellaneous

We observed in a foal a unique spinal cord malformation in the sixth through eighth thoracic segments associated with

a thoracic vertebral scoliosis (Fig. 2-21). The vertebral canal was enlarged through the scoliotic portion and contained a massive enlargement of the spinal cord, part of which was fluctuant and part firm. The fluctuant part contained CSF in a large syrinx. The firm part was a mass of normal-appearing but disorganized spinal cord parenchyma. Masses of gray matter with normal neurons and glia were intermixed with bundles of normal white matter processes. This was diagnosed as a combined hamartoma and myelodysplasia. Despite the remarkable focal disorganization of spinal cord parenchyma, this foal had no pelvic limb gait abnormality. Nature's surprises keep us humble and honest.

Chapter 3 INFLAMMATORY DISEASES OF THE CENTRAL NERVOUS SYSTEM

In this chapter, we have assembled the important, spontaneous, neurological diseases of animals that are marked by CNS inflammation. Many of these conditions are caused by infectious agents, such as viruses, bacteria, and protozoa; for other diseases, the etiology is unknown. Inflammation can be defined as a local reaction to injury, and to the histopathologist the hallmark of CNS inflammation is the influx of peripheral blood leukocytes into the neuroparenchyma and its coverings, sometimes accompanied by evidence of altered vascular integrity with edema and even fibrin effusion. We recognize that an important feature of inflammation of the brain and spinal cord is the reaction of intrinsic glial elements; however, these cells respond to changes in their environment in a variety of circumstances, such as following trauma and in the degenerative diseases.

In following these guidelines, a few syndromes are a problem: for example, the tissue reaction in the transmissible spongiform encephalopathies lacks the vital features of CNS inflammation, but this group of diseases is caused by atypical agents and this chapter seems to be the most appropriate one in which to house them. Other syndromes we discuss here are inflammatory but not primarily of the parenchyma; these are the vasculitides. Some are largely confined to the CNS (equine herpesvirus), whereas others are neural manifestations of what is usually a more widespread process (canine meningeal polyarteritis, malignant catarrhal fever).

RABIES

Rabies virus, an enveloped RNA rhabdovirus, is the cause of a lethal encephalomyelitis and ganglionitis in many areas of the world. The disease is endemic on all continents except Australia and has been successfully excluded or eradicated from some island states such as Great Britain, New Zealand, and Iceland. Rabies affects humans, domestic and

nondomestic animals, and other warm-blooded vertebrates. To understand rabies, it has been necessary to study the epidemiology of the infection in a variety of animal populations; indeed, it has required an examination of the ecology and population dynamics of several wildlife species.

Rabies is the most important zoonotic infection; it is well known that human recovery, once clinical signs develop, is exceptionally rare. Accordingly, in some countries, a tremendous investment of time, effort, and money is given to controlling this disease, for example, in the United States where human cases are of the order of only one or two per year. In 1980, a rabid dog in California bit 3 people, and 70 others who were exposed were identified. Fortunately, no persons or other animals were known to develop rabies from the episode, but the associated costs, including human antirabies treatment and animal vaccinations from this single rabid dog were \$105,790.¹ In some nations such as India and the Philippines, rabies accounts for thousands of human deaths each year. In South America, farm animal losses are considerable.

Rabies is a disease of exceptions, and this is perhaps best exemplified in its clinical manifestations. Thus, although a list of "typical" clinical features can be assembled, the diversity of presentations is in itself most typical of rabies. For example, within a group of 13 rabid horses, the initial tentative diagnoses include colic, lameness, tetanus, peripheral neuritis and ear ticks.²

Rabies is transmitted to animals by bite inoculation of virus in saliva. The incubation period before neurological signs develop is a second exceptional feature for this infection. The incubation may be little more than a week but generally is of the order of 1 to 3 months; cases up to 6 months are well known, and, exceptionally, incubation periods may exceed a year.^{3,4} The anatomical location of the

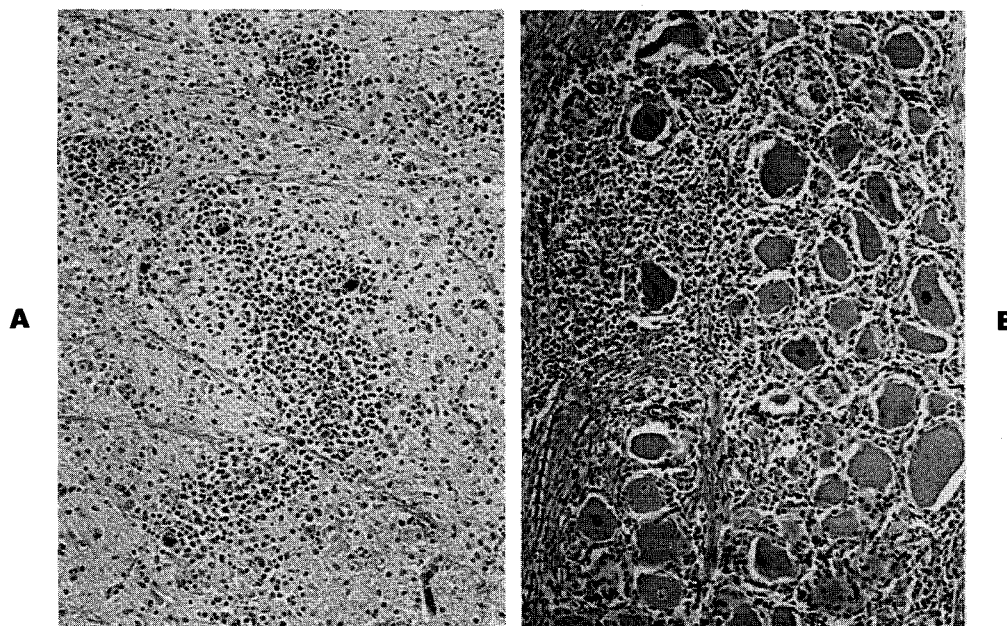


Fig. 3-1. Rabies, horse. **A**, Nonsuppurative encephalitis, medulla. (H&E, $\times 140$.) **B**, Nonsuppurative ganglionitis, trigeminal ganglion. (H&E, $\times 140$.)

bite has some bearing, as inoculations closer to the head result in a shorter incubation time than those at the periphery. A number of other parameters probably bear on the incubation, namely, viral strain, the quantity of virus inoculated, and host age and immune status.^{5,6} Some animals—for example, **swine**—may simply be found dead with no premonitory signs.⁷ Some infections are apparently aborted; such animals remain disease-free and have antibody to rabies virus. Recovery after neurological disease develops is much less common but has been described with street virus and vaccine virus-induced rabies.^{6,8,9}

Important clinical signs of rabies are an alteration of behavior, combined with various patterns of ataxia, and paresis or paralysis. For a domestic **dog**, acting in a peculiar way (restless or fearful and hiding) may be the first sign of abnormality,¹⁰ and abnormal behavior such as unusual friendliness may be manifest by wild animals. Rabies is often described as having “furious” and “dumb” forms; the former relates to episodes of aggressive and destructive behavior (including biting) that may be directed towards other animals, humans, or inanimate objects such as a leash or cage door. Furious behavior follows infection of limbic system neuronal populations in the brain.¹¹ The ingestion of soil or sand or the presence of foreign bodies in the stomach should also raise the suspicion of rabies.

Concurrent with this aberrant behavior, there may be muscle shivering or trembling, ataxia, and paresis or paralysis of limbs, jaw, or tongue. Pharyngeal paralysis may

result in profuse salivation, but such can also follow self-inflicted oral injuries. In dumb rabies, dogs are lethargic to stuporous, and biting is uncommon. Paralysis and seizures can follow either form. In **cattle** there is often paralytic disease with knuckling, sinking of the hind quarters, a flaccid tail, and hypoaesthesia of the hind quarters.¹² Paralysis and collapse follows. Continuous bellowing is sometimes noted in cattle with furious rabies; they show violent activity and are hyperesthetic to any stimulation. **Sheep** are usually passive and anorectic, although they may show aggression to their handlers or each other. **Horses** may show apparent lameness, progressing to signs of brain stem or ascending spinal cord disease and eventually recumbency.¹³ Some show maniacal behavior,¹² but variability of the presenting signs remains noteworthy.¹⁴ Clinical signs progress rapidly; rabies is usually fatal in 7 to 10 days and often in only 3 or 4.

The pathological changes of importance in rabies are microscopic, but important clues may be observed at the necropsy: evidence of injury or mutilation and the presence of alimentary foreign bodies. Histopathological findings are a nonsuppurative polioencephalomyelitis with craniospinal ganglionitis (Fig. 3-1). The combination of nonsuppurative inflammation of the CNS and ganglia has some diagnostic usefulness in most species except for the pig, in which it is seen with a variety of viral infections. (See the section about miscellaneous viral diseases of swine later in this chapter.) Inflammation is diffuse in the neuraxis, although somewhat

milder in the cerebral cortices than elsewhere. Lesions predominate in the gray matter or in populations of neuronal cell bodies. Perivascular cuffs are largely lymphocytic, and the parenchymal glial response is at first microglial but later mixed with astrocytes. The severity of these inflammatory changes varies widely; they may be severe in the dog and horse, with considerable neuronal degeneration, but minimal in cattle, and they do not correlate with the severity of neurological signs. Neuronal degeneration is often not severe although individual necrotic neurons undergoing neuronophagia will be found. Many harbor inclusion bodies but otherwise appear perfectly normal. Indeed, there is evidence from experimental infection in mice implicating an immunopathological basis for disease development.¹⁵ In skunks and foxes, rabies may produce a spongiform encephalopathy with vacuolation of gray matter neuropil remarkably similar to that seen in scrapie.^{16,17} Ultrastructurally, the vacuoles are membrane bound and often within dendrites. Negri bodies—single or multiple eosinophilic, ovoid, intracytoplasmic inclusions (Fig. 3-2, A)—may be found anywhere in the CNS, including retinal ganglion neurons, or in peripheral ganglia; conventional wisdom dictates that they are more readily encountered in cerebellar cortical Purkinje cells in ruminants and hippocampal neurons in carnivores. The frequency with which Negri bodies occur seems to be inversely proportional to the degree of inflammation. Ultrastructurally, the Negri body consists of a central, rather amorphous matrix with bullet-shaped particles within this matrix or budding from cellular membranes at the margins.^{6,18,19} Before contemporary microbiological techniques were developed, the identification of Negri bodies was of crucial diagnostic importance. Experience showed, however, that 15% to 30% of rabies virus infections (with so-called street virus) do not incite the formation of inclusions. Furthermore, killing a rabid animal, thus abbreviating the clinical course, may also result in a case that lacks Negri bodies. Equally important has been the documentation of pseudo-Negri bodies: inclusions found in normal animals or perhaps formed nonspecifically in other diseases that can be confused with rabies virus inclusions. Such include neuronal inclusions in the lateral geniculate nucleus²⁰ and pyramidal cells of the hippocampus of cats, eosinophilic bodies in Japanese brown beef cattle,²¹ hippocampal inclusions in moose,²² brain stem inclusions in woodchucks (Fig. 3-2, B),²³ and the cytoplasmic lamellar body of dogs (Fig. 3-2, C and D), in which stacked and condensed cisternae derived from granular endoplasmic reticulum produce discrete eosinophilic intracytoplasmic inclusions, particularly in thalamic and cerebellar cortical Purkinje neurons.²⁴⁻²⁶

The diagnosis of rabies now rests on the use of brain tissue for immunofluorescent procedures²⁷ and transmission to neonatal mice by intracerebral inoculation. Virus may also be demonstrated in peripheral tissues, for example, in

the cornea. Rabies viral antigen can be demonstrated immunocytochemically in formalin-fixed, paraffin-embedded tissue (Fig. 3-3).^{28,29}

Rabies is usually transmitted by traumatic inoculation of virus in saliva from an infected carnivore; thus infection in many species (human, horse, cow) is a dead end with respect to further passage except for transplacental infection, which has occurred in cattle.⁴ Aerosol infection has taken place in bat caves, where the density of airborne virus particles is exceptionally high, and in laboratory accidents. Bats, including insectivorous, fructivorous, and vampires, are all implicated in rabies spread in the Americas. Vampire bat rabies presents yet one further exceptional feature in that these animals may be disease-free and yet shed virus in their respiratory secretions and saliva for many months; in South America in particular, a significant proportion of rabies is transmitted by vampire bats. Finally, it is worth noting that the oral route is employed to vaccinate wildlife by way of vaccine virus in baits.

The important studies by Murphy et al³⁰ have shown that, following inoculation of the virus, there is an initial phase of replication in myocytes. It is proposed that viral entry into muscle is mediated by the viral glycoprotein binding with the acetylcholine receptor site at the neuromuscular junction,³¹⁻³⁴ although there are probably other cellular receptors. Virus then passes to axon terminals of motor neurons and to the neuromuscular and neurotendinous spindles that allow access to sensory axon terminals. Virus then moves centripetally by retrograde axoplasmic flow in motor neurons to the spinal cord ventral horn or to brain stem motor nuclei, and over sensory neurons to craniospinal ganglia and hence to the CNS. Experimental manipulations show that the pathway followed to the CNS (motor and/or sensory) varies with the rabies virus strain and probably other factors, such as the site of inoculation.³⁵ Direct access to nerve endings, without a premonitory phase of replication in muscle, has also been proposed.³⁶

Within the CNS, the primary role of axonal transport (rather than of extracellular routes) for rabies virus spread has also been demonstrable, for example, with inhibitors of axoplasmic flow such as colchicine.³⁷ Dispersion from neuron to neuron occurs across synapses, and virus disseminates widely in the brain and spinal cord. The perturbing effects of the infection are particularly marked within the limbic system, which is concerned with behavior. Thus aggressiveness (and biting) is not a chance effect but reflects viral adaptation, which serves to enhance the likelihood of transfer of the agent.¹¹ From the brain and spinal cord, there is a third phase with centrifugal spread along peripheral nerves to many organs including the main viscera, skin, eyes, brown fat, and salivary glands. Virus replicates in salivary acinar epithelium and buds into the lumen.

The prolonged incubation period seen in some cases of rabies may partly result from a latent phase with virus in

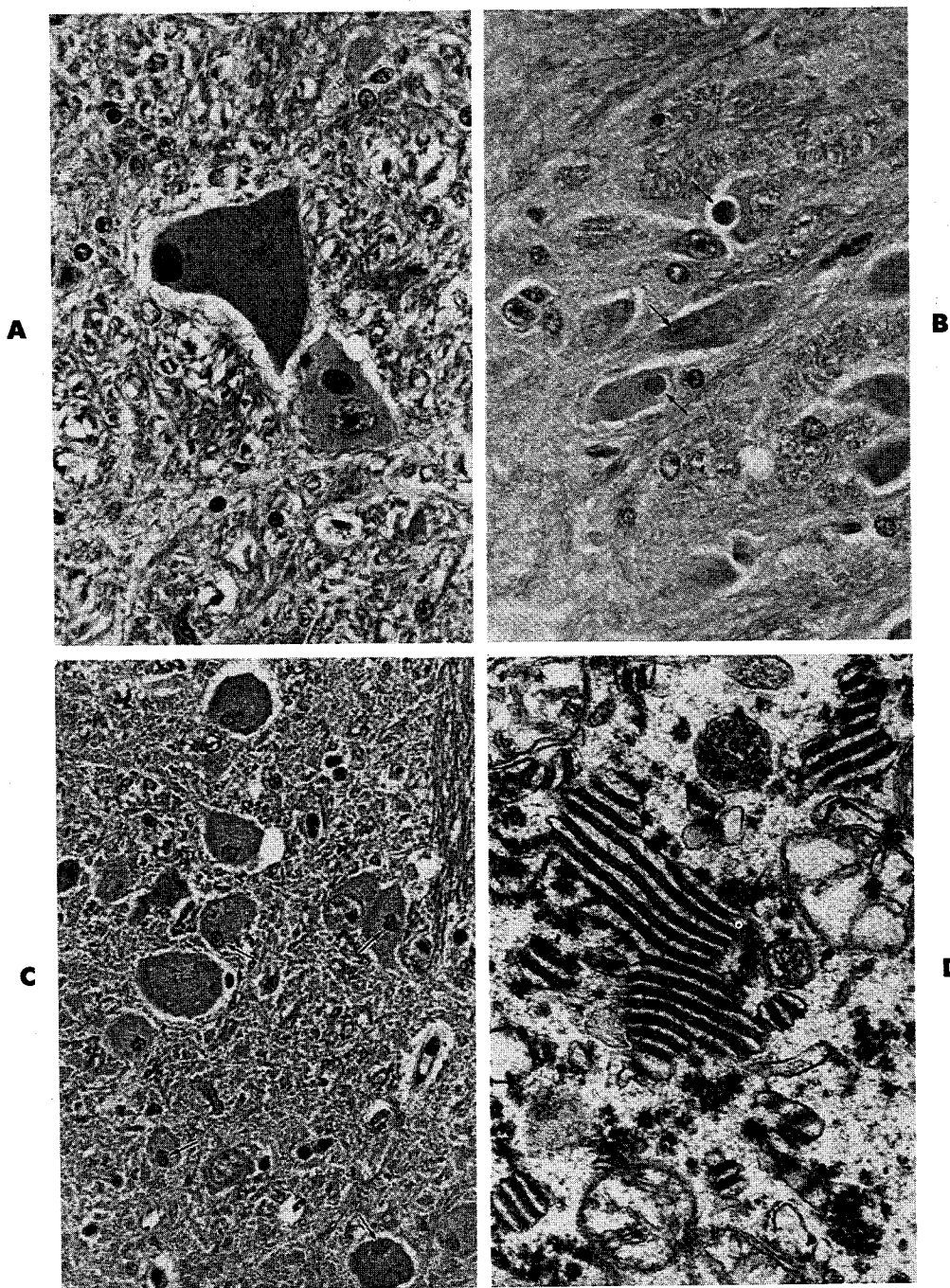


Fig. 3-2. A, Rabies. Cytoplasmic inclusions (Negri bodies) in neurons of the medulla, cow. (H&E, $\times 560$.) B, Pseudo-Negri bodies in woodchuck brain (*arrows*). (H&E, $\times 560$.) C, Cytoplasmic lamellar bodies. Inclusions (*arrows*) in thalamic neurons, dog. (H&E, $\times 560$.) D, Electron microscopic detail of lamellar body, Purkinje cell, goat. ($\times 56,250$.)

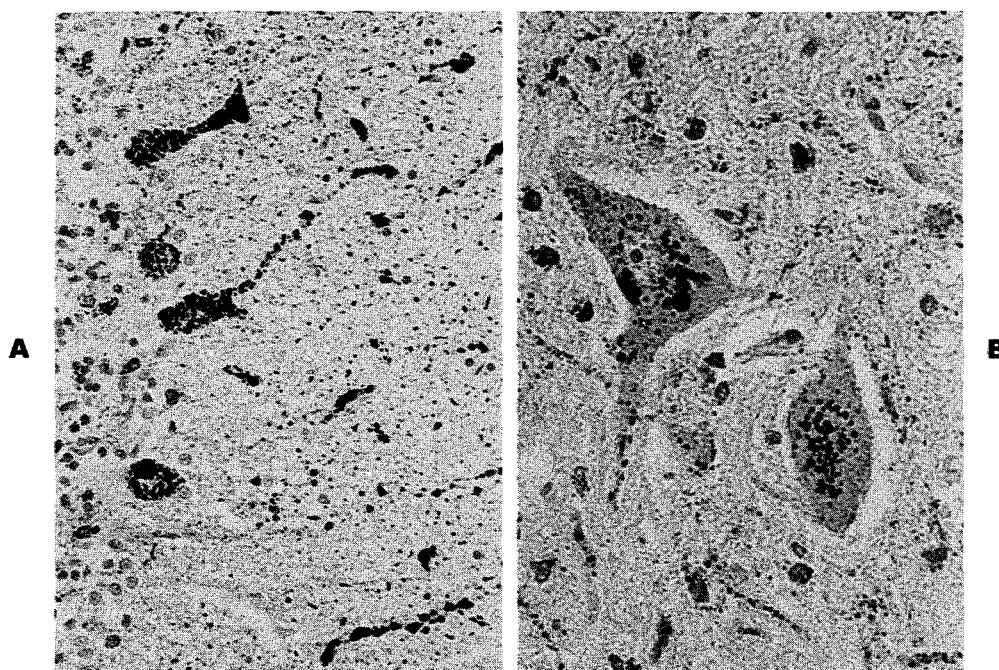


Fig. 3-3. Immunocytochemical demonstration of rabies viral antigen, raccoon. A, Purkinje cells in cerebellar cortex. ($\times 350$.) B, Cerebellar nucleus. ($\times 560$.)

myocytes, but progression of events can probably be blocked at subsequent points also. This first step is probably crucial in determining whether the infection progresses or is aborted by prebite or postbite acquired immunity. The pure neurotropism of the agent is shown by the restriction of pathological effects of the virus to cells of the CNS. Rabies virus isolated from one host may have a varied pathogenicity for others, probably reflecting some degree of selection ("fixation"), which occurs with continuous cycling within a single host species in nature. Experimentally, the same end is achieved by repeated passage by intracerebral inoculation. Diminished pathogenicity may result from changes in the viral glycoprotein, as this structure appears to be important for neurovirulence.⁵ Monoclonal antibody analysis of rabies isolates does reveal viral strain differences,³⁸ which also raises the question of whether immunity is strain-specific.

Epidemiological studies of rabies point to persistence of the agent in urban and sylvatic (wildlife) animal populations.⁴ The urban cycle depends largely on domestic and stray dogs and cats and diminishes in importance with population control and vaccination. The dog, however, remains of crucial importance worldwide as a vector for transmitting rabies to humans, especially in developing countries.⁶ The options for rabies elimination in countries with canine rabies infection, and the importance of economic factors in the choice of action, have been reviewed.³⁹ In contrast to developing countries, most rabies in the United States occurs in wildlife.⁴⁰ The sylvatic cycle relates to endemic infection

of wildlife, which, once established, is very difficult to eradicate. In continental Europe, the red fox, which is highly susceptible to rabies, is of prime importance, acting both as vector and reservoir.⁴¹ Extensive oral vaccination programs, employing baits that contain rabies vaccine virus, have been used in Europe, aimed specifically at the red fox population; future campaigns may utilize recombinant virus.⁴¹⁻⁴³ Foxes are important in the United States also, but here the skunk is the major reservoir. Regionally, specifically in the eastern states, the raccoon is important also and is of concern because of its habit of associating with humans to scavenge from household garbage.⁴⁴ Elsewhere, mongooses, wolves, jackals, and other species are of local importance. These wildlife species are responsible for domestic animal and human infections;⁴⁵ for a comprehensive review of the epidemiology and other aspects of rabies, see King and Turner.⁴⁶

Postvaccinal rabies may occur if vaccination is performed at the time of surgery or other stress. Vaccines may be lethal in species for which they are not approved; sometimes appropriately used rabies vaccine induces encephalitis,^{9,47} perhaps most commonly in the cat.

References are on page 171.

AUJESZKY'S DISEASE

Aujeszky's disease is a common, sometimes endemic viral infection of the pig that occurs sporadically in other species. It is recognized in most parts of the world. The

etiological agent is *Herpesvirus suis*, and infection of the pig takes several forms. Susceptible sows infected during pregnancy may suffer early embryonic deaths or abortion, sometimes expelling mummified fetuses. In young piglets the mortality rate is very high; postweaning growing pigs are more resistant, and in older stock the infection is mild or may be inapparent. Adult pigs may be latently infected and shed virus. Rodents have also been suggested as a source of infection. In other domestic animals the infection is peracute and fulminant. Rabbits are susceptible to experimental infection and often have been used, in transmission studies, to confirm a presumptive diagnosis of Aujeszky's disease.

Aujeszky's disease in 5- to 6-week old pigs was studied by Dow and McFerran.¹ Clinical signs, evident 5 to 6 days following infection by the intranasal route, included pyrexia, ataxia, tremors, nystagmus, recumbency, and generalized seizures. Signs of respiratory tract involvement may also occur.² In younger piglets, acute death may occur before neurological signs are seen. Pruritus, a hallmark of the syndrome in nonporcine species (hence the pseudonyms pseudorabies and mad itch), is not seen in the pig. Neuropathological findings are of a nonsuppurative ganglionitis and meningoencephalomyelitis, particularly affecting cerebral and cerebellar cortices. In the cerebral cortex there is a multifocal, patchy, microglial proliferation about individual chromatolytic or shrunken, dark, necrotic neurons (Fig. 3-4, A); this progresses to neuronophagia. These changes are accompanied by an influx of lymphocytes, macrophages, and the occasional polymorphonuclear cell in the neuroparenchyma and leptomeninges. In areas of parenchymal necrosis, neutrophils are more numerous.³ Involvement of the cerebellar cortex includes leptomeningitis, patchy necrosis of granule and Purkinje cells, and microglial cell proliferation in the molecular layer, producing the so-called glial shrubbery due to the clustering of these cells on Purkinje cell dendrites. Lesions of varying severity are found in the basal nuclei, thalamus, hypothalamus, pons, medulla, and, usually less so, the spinal cord. Intranuclear inclusion bodies, characteristic of some herpetic infections, may be difficult to find. Dow and McFerran¹ observed inclusions in approximately a third of natural or experimental cases of Aujeszky's disease in the pig. Inclusions vary from homogeneous eosinophilic bodies that fill the nucleus to multiple small globules. They occur in neurons and glia early in the course of the infection. Viral antigen and nucleic acid can be demonstrated by immunocytochemistry and in situ hybridization, respectively.^{4,5}

Herpesvirus suis is neurotropic, and damage predominates in gray matter. However, glial foci are seen in white matter adjacent to primary lesion areas, and necrosis of folial white matter in the cerebellum may occur. In the cranial and spinal ganglia, necrotic ganglion cells are marked by satellite Schwann cell proliferation and by mixed polymorphonuclear and lymphoid cell infiltrates.⁶

Infection of nonporcine species is peracute with high

mortality. These are end-stage hosts, unimportant in viral spread to other animals. Their pattern of microscopic changes in the brain varies with the route of infection, unlike the pig, in which panencephalitis is the rule. Infection of **dogs and cats** is perhaps most frequent, but episodes in cattle, sheep, and goats are well known. Infected dogs and cats may die suddenly without premonitory signs.⁷ Most run a peracute clinical course of approximately 24 to 48 hours, marked by rapid respiration, fever, salivation, vomiting, ataxia, and seizures. Excessive salivation, a very common observation,⁸ probably marks the onset of bulbar paralysis, which leads to death with respiratory failure. Intense pruritus, generally of the head and facial region, results in persistent and even maniacal excoriation to the point of self-mutilation. This well-known clinical feature of Aujeszky's disease is not inevitably observed in dogs and cats⁷⁻¹⁰ and was lacking in **horses** with Aujeszky's disease.^{11,12}

Pathological findings in dogs and cats (Fig. 3-4, B through D) are qualitatively similar to those in swine but differ in their distribution. Thus, although there is nonsuppurative ganglionitis and encephalomyelitis, it particularly affects the caudal brain stem. Neuronal degeneration and neuronophagia are observed within the spinal and myenteric ganglia,⁹ spinal cord gray matter (particularly the dorsal gray columns),¹³ medulla, and pons. Neuronal degeneration or necrosis may be found in the hypoglossal, dorsal vagal, and pontine nuclei. Karyorrhexis of the inflammatory infiltrate and reactive microglial cells is a feature of the lesion in carnivores. Experimental oral infection of the cat¹⁰ produced early lesions of the solitary nucleus and tract, area postrema, and pathways of sensory branches of the ninth and tenth cranial nerves. Overall, lesions were most consistently found in the medulla and extended rostrally to the thalamus and caudally throughout the spinal cord in a patchy fashion. Intranuclear eosinophilic inclusions, single or multiple as in the pig, may be found in neurons.

In **cattle**, there may be sudden death, but pyrexia, severe pruritus (sometimes with repeated licking of the skin), tremor, seizures, and coma are more common prior to death.¹⁴ The clinical course is often 24 hours or less after a variable incubation period; subcutaneous inoculation in the cheek is more quickly lethal than inoculation of skin over the hip. In young calves, pruritus may be absent. Sequential experimental studies in calves inoculated subcutaneously revealed a localized spinal ganglionitis and poliomyelitis.¹⁴ Lesions were more severe ipsilaterally than contralaterally in ganglion and spinal cord, and pathological changes in the dorsal gray columns of the spinal cord were more severe than those of the corresponding ventral columns. Myelitis progressively extends rostrally as far as the medulla and also caudally but is less necrotizing than in the primary segment, whose sensory fibers supply the field of virus inoculation. Inoculation into the cheek produces a trigeminal ganglionitis with central lesions focused in the spinal tract and nucleus of this cranial nerve. In contrast,

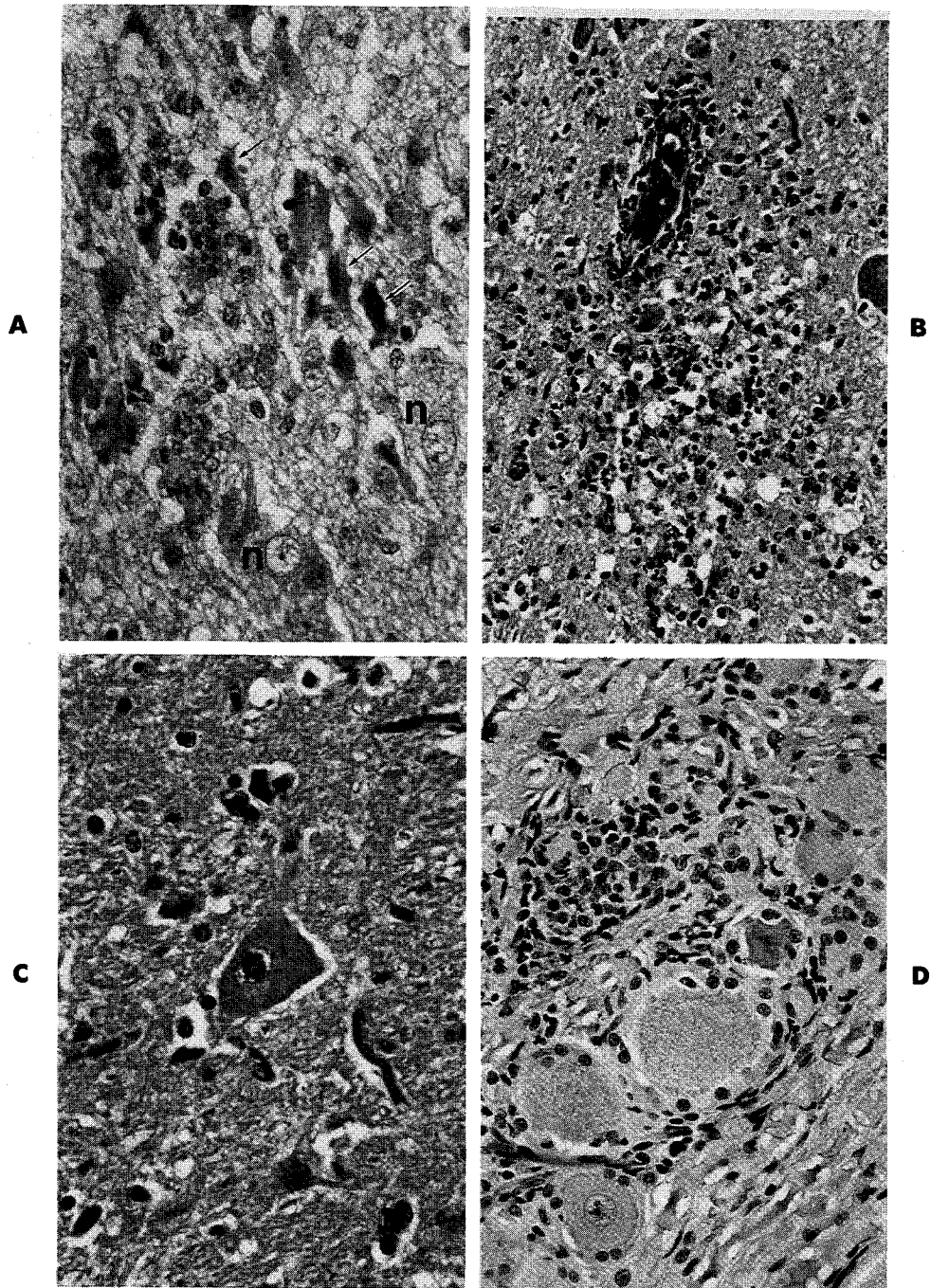


Fig. 3-4. Aujeszky's disease. **A**, Pig. Acute neuronal necrosis (*arrows*) and focal gliosis in olfactory cortex. A few neurons (*n*) are preserved. (H&E, $\times 560$) **B**, Dog. Necrotizing encephalitis, thalamus. Note disintegration of the inflammatory cells. (H&E, $\times 350$.) **C**, Dog. Neuron with intranuclear viral inclusion, thalamus. (H&E, $\times 560$.) **D**, Cat. Nonsuppurative ganglionitis, cervical spinal ganglion. (H&E, $\times 350$.)

intranasal exposure of calves results in a necrotizing frontal lobe encephalitis that diminishes progressively through the brain stem. In either pattern of infection (subcutaneous or intranasal), ganglion cell changes in craniospinal ganglia and in the CNS vary from mild chromatolysis to necrosis marked by pyknosis and basophilia; neuronophagia may be observed. Large pyramidal neurons of the cerebral cortex are often affected, and there is an attending microgliosis. Inclusions are most readily found in more mildly injured neurons in the CNS and ganglia. They are common also in glia and infrequently found in satellite cells. Perivascular and leptomeningeal inflammation in the CNS and interstitial infiltrates in the ganglia are often mixtures of neutrophils, lymphocytes, and macrophages. Ultrastructural examination¹⁵ revealed viral capsids or complete particles within the axoplasm of peripheral nerves, within neurons, and occasionally in Schwann cells and monocytes in the spinal ganglia. Neuronal degeneration was marked by early nucleolar disruption and progressive loss of organelles, such as the Nissl bodies, from the perikaryon.

Consistent with its neurotropic properties, this herpesvirus gains access to motor neurons in the brain stem by retrograde axonal transport¹⁶ and ascends sensory afferent fibers of the spinal and cranial nerves. Although viral transfer along peripheral nerves in Schwann cells, endoneurial cells, interstitial lymph or by axonal transport have all been debated, the evidence favors the axonal pathway.¹⁷ Anterograde transport can also be demonstrated (for example, following intraocular inoculation), and there are highly specific pathways of transneuronal dissemination within the CNS.¹⁶ Infection can probably occur by several routes including peripheral abrasion, contamination of a skin wound, across the nasal mucosa,¹⁸ and by the alimentary route. The last mentioned is of importance in dogs and cats with access to infected pig fetuses, swine offal, or pig meat. In cats, the tonsils may be the portal of entry.¹⁰ Evidence for vaginal infection of cattle is recorded.¹⁹ Pruritus of ferocious intensity is characteristic but not invariable; its development coincides with the appearance of inflammation in the ganglion and central sensory gray matter.²⁰

In its primary host, the pig, this agent seems to act much like herpesviruses in other animal species; it produces in utero infection with fetal losses and disseminated infection with panencephalitis in the neonate to which resistance is progressively acquired with maturity. However, in nonporcine species the virulence and neurotropism are enhanced, resulting in peracute infection and rapid death. In fact, the presence of Aujeszky's infection in a pig herd may first be manifest by clinical disease in a farm dog or cat.

References are on page 172.

CANINE DISTEMPER ENCEPHALOMYELITIS

Canine distemper (CD) is an infectious viral disease of the dog and its relatives (e.g., wolf, fox, and coyote). In-

fection and disease also occur in the Mustelidae (ferret, mink, skunk, weasel, otter) and the Procyonidae (raccoon, panda); in seals, dolphins, and porpoises (mostly caused by closely related distemper viruses); in javelinas; on rare occasions in large cats (lions, tigers, leopards); and perhaps even in nonhuman primates.¹⁻⁷ Efficacious vaccines for use in the domestic dog have been available since the 1960s and have dramatically reduced the incidence of this disease. However, CD remains an important cause of morbidity and mortality in unvaccinated dog populations and appears sporadically in dogs with an apparently adequate vaccinal history. Ironically, and perhaps inevitably, the time since the 1960s (when effective control of CD has been possible) has been one of the most active periods for basic research into CD and, in particular, canine distemper encephalomyelitis (CDE). However, we should also recall that several comprehensive descriptions of the neuropathological features of this disease were published well before 1900.⁸

CD is caused by a *Morbillivirus* (family Paramyxoviridae) and is closely related to human measles virus, rinderpest virus of cattle, and peste des petits ruminants virus of sheep and goats. Several strains or biotypes of CD virus have been isolated from diseased dogs and subsequently characterized in experimental infections (virulent viruses) or have been produced by the adaptation of wild type virus to tissue culture (attenuated viruses). There is but one serotype, however, and so exposure to one strain protects dogs against any subsequent challenge. The concept of virulent and attenuated viruses is relative rather than absolute; for example, intracerebral inoculation of "avirulent" tissue culture-adapted virus into susceptible newborn puppies induces a fatal encephalitis. Furthermore, it appears that on rare occasions vaccinal virus (administered appropriately) can produce a fulminating encephalitis in dogs.⁹⁻¹¹ In contrast to the dog, for which it is intended, modified-live vaccine virus is commonly lethal if administered to some CD-susceptible animals such as black-footed ferrets and the lesser panda.^{12,13}

CD is common in dogs in the first year of life, but many cases are seen in adults.¹⁴ Infection occurs by the respiratory route and, rarely, prenatally across the placenta.¹⁵ It has been recognized for decades that neurological disease in CD may be preceded by a generalized, catarrhal illness or may appear de novo, the systemic phase being mild and unnoticed. This systemic stage is marked by immunosuppression¹⁶ (probably due to both direct viral effects and to suppressor cell activity)^{17,18} and by catarrhal inflammation, particularly of the respiratory and gastrointestinal tracts. Studies in specific pathogen-free dogs suggest that infection of the CNS occurs early in the systemic phase,¹⁹ probably in most, if not all, infected dogs. Thus cases of CD that progress from systemic to neurological illness apparently do so because of a failure to clear the early viral invasion of the brain and spinal cord. A clear correlation between the prompt devel-

opment of cell-mediated antiviral immune responses and recovery from infection has been shown.^{20,21} However, all facets of the immune repertoire including antiviral antibodies,²²⁻²⁶ natural killer cells,²⁷ and antibody-dependent cell-mediated cytotoxicity²⁸ are probably recruited to combat the disease. In some animals, virus successfully persists in the CNS, and this is associated with a diminished expression of viral surface polypeptides in the lesions.²⁹

Signs of neurological disorder in CD are diverse. Experimentally, the clinical course and neuropathological patterns of the encephalomyelitis can be shown to vary with the virus strain³⁰ and age at the time of infection.³¹ In 3-month-old pups, the Snyder Hill strain of CDV induces an acute polioencephalomyelitis, whereas infection with the R252 and A75-17 strains results in subacute to chronic CNS disease in which degeneration and inflammation in white matter predominates and neuronal injury is milder. Consequently, the presenting clinical signs may range from depression, abnormal behavior, or seizures—reflecting involvement of gray matter in the cerebral hemispheres—to general proprioceptive ataxia and spastic paresis from brain stem or spinal cord lesions, vestibular disorders from medullary or cerebellar lesions, or cerebellar ataxia. A chronic, relapsing clinical course has been described in one case³² but is exceptionally rare.

Neurological examination commonly reveals asymmetrical deficits and often implicates multifocal disease, both of which are valuable clinical observations. One characteristic residual sign of CDE is myoclonus, typically involving masticatory muscles or a single limb. This repetitive, rhythmical muscle contraction is believed to be due to the establishment of an autonomous pacemaker at the level of the lower motor neuron. However, pathological changes in the appropriate segment of brain stem or spinal cord gray matter are usually surprisingly mild.

The clinical diagnosis of CDE can present a considerable challenge. Evidence of multifocal disease on the basis of the neurological examination is helpful. Funduscopic changes (from chorioretinitis) frequently accompany the neurological disease, and we have noted that some dogs with subacute to chronic forms of CDE have prominent congested scleral blood vessels, reflecting inflammation in the anterior uvea.³³ Elevated levels of protein and mononuclear cells in the CSF are common and only rarely are lacking. These cells should be carefully examined for cytoplasmic inclusion bodies, although their detection is rare.³⁴ Under experimental conditions, CDV antigen has been demonstrated in CSF macrophages and lymphocytes in lethally infected dogs up 5 weeks after infection^{22,35} but is less likely to be found in more persistent infections. Specific antiviral antibody is present in CSF in some chronic cases of CDE,^{30,36} and the presence of interferon in CSF is a valuable marker under experimental conditions.³⁷ At necropsy, virus isolation can be attempted if facilities are available (often

explant cultures of brain are most successful), and viral proteins can be demonstrated immunocytochemically in the neural and extraneural lesions.³⁸⁻⁴¹

At autopsy, gross lesions occur in the white matter form of CDE with sufficient frequency to warrant a careful examination. Such changes are seen as areas of softening and brownish discoloration, sometimes accompanied by hemorrhage. Histopathological changes often involve both gray and white matter but usually predominate in one or the other. The earliest tissue changes are degenerative and inflammation follows; usually, but not always, evidence of both can be found. For convenience of discussion, the patterns of microscopic alteration can be subdivided into two main categories: gray matter disease and white matter disease.

In **gray matter disease**, neuronal degeneration, gliosis, and lymphoplasmacytic inflammation occur in the cerebral and cerebellar cortices, basal nuclei, brain stem, and spinal cord. These changes can be remarkably mild, especially in young puppies, despite a severe, fulminating neurological illness with seizures. However, CDV infection of neurons, as shown by immunocytochemistry, may be extensive. If the clinical course is brief and there are only minimal degenerative changes, the lesion can be designated an encephalopathy. Neuronal infection results in dilation of the endoplasmic reticulum and Golgi cisternae, detachment of ribosomes from the granular ER, and mitochondrial degeneration.⁴² Viral nucleocapsids occur in the perikaryon or processes, often in proximity to synapses that may disturb neuronal excitation and inhibition.

Infection at first incites mild capillary endothelial swelling and hyperplasia and a localized proliferation of rod cells (microglia) (Fig. 3-5). Lightly acidophilic viral inclusions are found, often with some difficulty, in the nucleus or cytoplasm of neurons and occasionally in nearby astroglia. Individual neurons undergo pyknosis and shrinkage, followed by satellitosis and neuronophagia,⁴³ and there is a secondary Wallerian degeneration.⁴² With time, a mild hematogenous, nonsuppurative inflammatory response develops in such areas of parenchymal injury and in the adjacent leptomeninges. Very rarely, the subarachnoid space contains syncytia of meningotheial cells,⁴⁴ reflecting the activity of the viral envelope fusion protein. Sometimes in the cerebral cortex, neuronal infection has a laminar pattern.^{30,45}

On rare occasions, CDE is associated with severe seizure activity and, at necropsy, a bilateral polioencephalomalacia involving the pyriform lobes, hippocampus, and related structures.^{46,47} However, a similar pattern of neuronal necrosis has been observed in other dogs with seizures, unrelated to CD infection.⁴⁸ Although in such cases of CDE some neurons in the areas of encephalomalacia harbor the virus, it is more likely that this selective necrosis of the rhinencephalon is a consequence of the seizure activity; similar lesions are seen in humans with severe epilepsy.

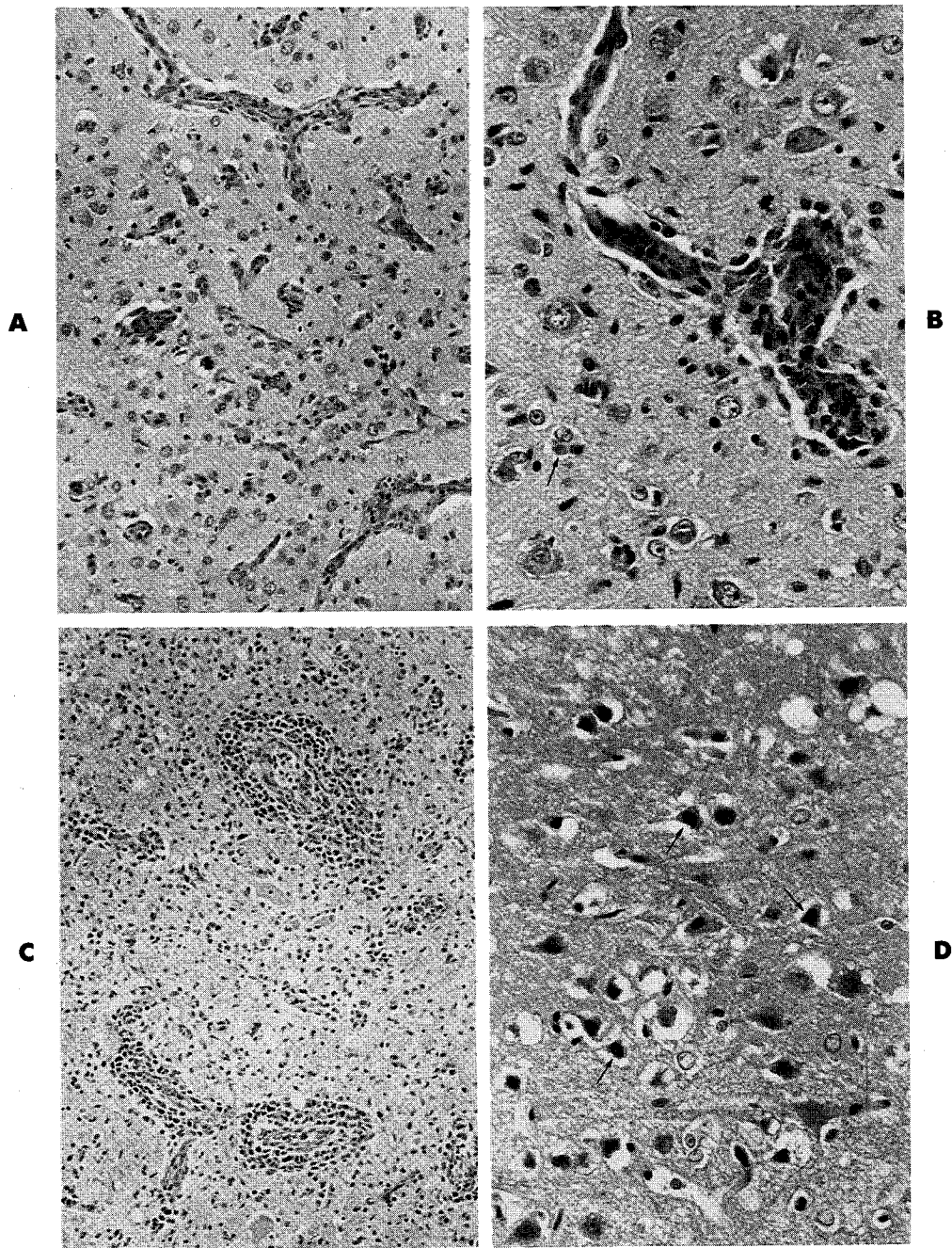


Fig. 3-5. Canine distemper encephalitis. Grey matter lesions. **A**, Dog. Hypertrophy of blood vessels, cerebral cortex. (H&E, $\times 180$.) **B**, Dog. Perivascular cuff and microglial cell proliferation. Cytoplasmic inclusion body (*arrow*) in a glial cell. (H&E, $\times 560$.) **C**, Dog. Lymphocyte and plasma cell perivascular cuffs and diffuse gliosis, medulla. (H&E, $\times 350$.) **D**, Ferret. Laminar cortical necrosis in canine distemper, probably seizure related. Arrows indicate ischemic neurons. (H&E, $\times 350$.)

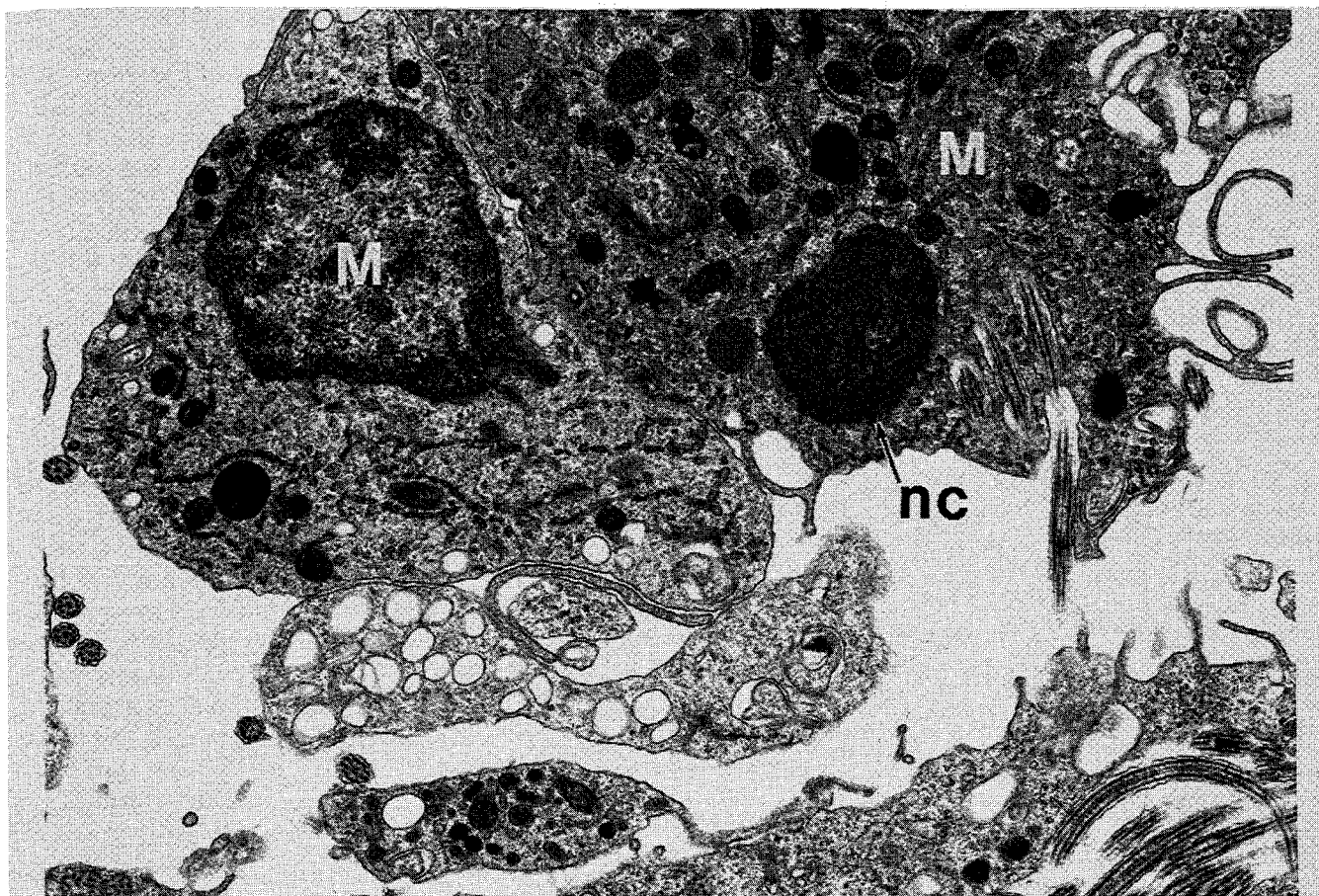


Fig. 3-6. Canine distemper encephalitis. Macrophages (*M*) within the fourth ventricle are entwined with cilia from the underlying ependymal cells. Note canine distemper viral nucleocapsids (*nc*) in a macrophage. ($\times 13,900$.)

This neuronal death could result from local ischemia (hypoxia/hypoglycemia) and may be mediated by excitotoxic neurotransmitters (see studies of measles encephalitis in mice.⁴⁹) Not all dogs that have seizures develop polioencephalomalacia; for example, mature dogs with idiopathic epilepsy typically do not have changes in the CNS. The factor that determines when seizures will result in such lesions may be the animal's age; in CD, this complication is more commonly seen in dogs under 1 year.^{46,47}

In **white matter disease**, lesions of the white matter are typically multifocal and more numerous than indicated by the clinical signs on a neurological examination.¹⁴ There is a predilection for the cerebellar peduncles, rostral medullary velum, optic tract, hippocampal fornix, and spinal cord white matter, which is explained by the proximity of these tracts to CSF. Productive viral infection has been demonstrated in the ependymal and choroid plexus epithelium,⁵⁰ and it seems that viral dissemination in CSF (Fig. 3-6), leading to infection of white matter adjacent to the covering

ependymal or pial layer, accounts for this pattern of myelin injury in the brain and spinal cord. The EM features of a CDV-infected macrophage are shown in Figure 3-6; one must be wary of tubuloreticular inclusions (Fig. 3-7),⁵³ which have been mistaken for CDV.

Gross lesions in the white matter are usually evident only in chronic cases in which lymphocytic inflammation is extensive, resulting in considerable demyelination and/or necrosis. White matter lesions initially are purely degenerative, with a mixture of primary demyelination (with axon sparing) and concurrent axonal and myelin injury. With time, a nonsuppurative inflammatory component is superimposed on the lesion.⁵¹⁻⁵³ Early changes begin with a swelling and hyperplasia of astrocytes and some microglial proliferation, often in (but not limited to) subpial and subependymal white matter. Many of these glial cells contain viral antigen.⁴⁵ Myelin loss is first seen as ballooning of individual sheaths, which, when many are similarly affected, produces a spongy, pallid zone of demyelination (Fig. 3-8).⁵⁴ De-

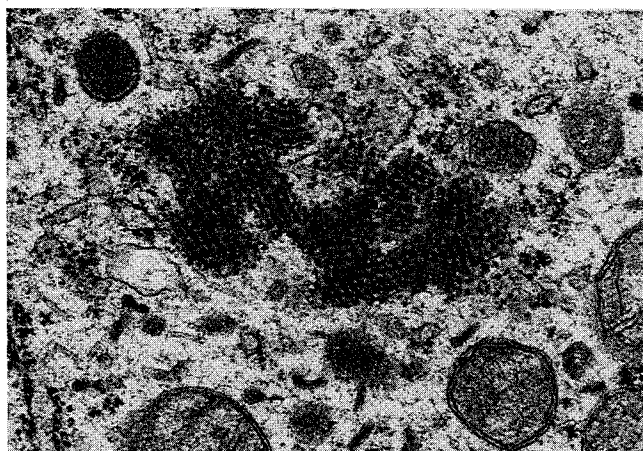


Fig. 3-7. Tubuloreticular inclusions. These paracrystalline arrays, which aggregate within the rough endoplasmic reticulum, have been mistaken for canine distemper and other viruses. ($\times 53,350$.)

myelination in CDE, evident about 21 to 24 days after infection,^{45,53} very typically has this spongiform appearance and morphologically more closely resembles some toxic myelinopathies or metabolic encephalopathies than the lesions of multiple sclerosis with which it has sometimes been compared. Loss of myelin proteins can be demonstrated immunocytochemically;⁵⁵ if conventional histochemical stains, such as luxol fast blue, are applied, the vacuolated areas are pale, indicating that myelin has been depleted. It is important to appreciate that the latter procedure does not discriminate between primary and secondary demyelination, which is best resolved by EM examination. Ultrastructurally, ballooned myelin sheaths are found to have split open at the intraperiod line;⁵⁰ free myelin fragments are phagocytosed—mainly by microglial cells, less so by astrocytes, and rarely by oligodendroglia⁵⁴—and compact myelin is stripped by the processes of macrophages (Fig. 3-9).^{51,56} Naked axons are readily found, but not all are normal; some are swollen with amorphous dense bodies, mitochondria, and vesicles and qualify as spheroids.⁵⁷ There may be some remyelination,⁵⁰ but it is not conspicuous.

In white matter lesions, intranuclear and intracytoplasmic viral inclusion bodies are present within astrocytes, and surface ependymal cells and these infected cells sometimes form syncytia.⁴⁴ Astrocytic infection is very common.⁵⁸ Indeed, in white matter, these cells appear to be the main target for the virus. Macrophages are very often infected also, but appreciating this usually requires EM examination. Based on conventional ultrastructural studies, the evidence of oligodendrocyte infection is scant,^{56,59} certainly in comparison with the ease with which viral nucleocapsids are found within astrocytes, microglia, ependyma, and neurons. Immunocytochemical preparations for the viral proteins

(Fig. 3-10) reveal infection of small clusters of glial cells in early white matter lesions and at the margins of large spongiform plaques that centrally contain less antigen. The presence of intranuclear inclusions is somewhat of a paradox for a virus that replicates in the cytoplasm. Oglesbee and Krakowka⁶⁰ have shown that this can be explained by a cellular stress response triggered by the infection. The induced heat shock protein leads to the translocation of viral N protein into the nucleus, where it is associated with nucleolar structures known as nuclear bodies.

In dogs that do not succumb during the early stage of white matter injury, a nonsuppurative inflammation develops within or near such lesions. This delayed inflammatory response presumably occurs when viral immunosuppression is waning. Perivascular spaces are progressively distended with lymphocytes, monocytes, and a few plasma cells. As large numbers of these cells migrate into the spongiform, astrogliotic white matter, the character of the lesion changes from demyelinating to necrotizing.⁵¹ The target for these mononuclear cells appears to be virus, and it seems that this inflammatory wave is capable of clearing the infection from the lesion.⁶¹ In contrast to areas of early myelin injury, inflammatory white matter lesions contain fewer glial cells positively labelled for viral antigen.⁴⁵ However, this inflammatory response may be a two-edged sword; dogs at this stage of the infection usually have subacute to chronic progressive neurological disease, and ongoing tissue damage may result from lymphokines and monokines released by these mononuclear cells.

The pathogenesis of CDE has been extensively studied in dogs and other susceptible species. Virus is carried into the CNS approximately 1 week after infection by virus-infected lymphocytes, monocytes, and platelets.^{19,62,63} The course of the infection from this point depends upon the animal's age, perhaps its genetic makeup, and the strain of the infecting virus. Spontaneous cases of CDE show a mixture of gray and white matter injury, although one pattern often predominates. Pure gray matter disease is rare but when observed usually occurs in young puppies. The sequence of events leading to injury to neurons and glial cells and, in particular, the mechanism of demyelination in CDE remain areas of active investigation. Potential candidates are the virus itself, cytotoxic immune responses to virus-infected cells, and autoimmune reactions to neural elements such as myelin. The early phases of the encephalomyelitis can be related to direct effects of the agent itself, most clearly in producing neuronal infection and degeneration.⁶⁴ The initial white matter damage also is distinctly associated with the presence of virus in the tissue, but exactly how primary demyelination is effected remains uncertain. Higgins et al⁵⁰ made the important observation that in CDE myelin loss from an axon can be segmental, involving one internode while sparing adjacent internodes; this pattern implicates a selective insult to the oligodendrocyte or the mye-

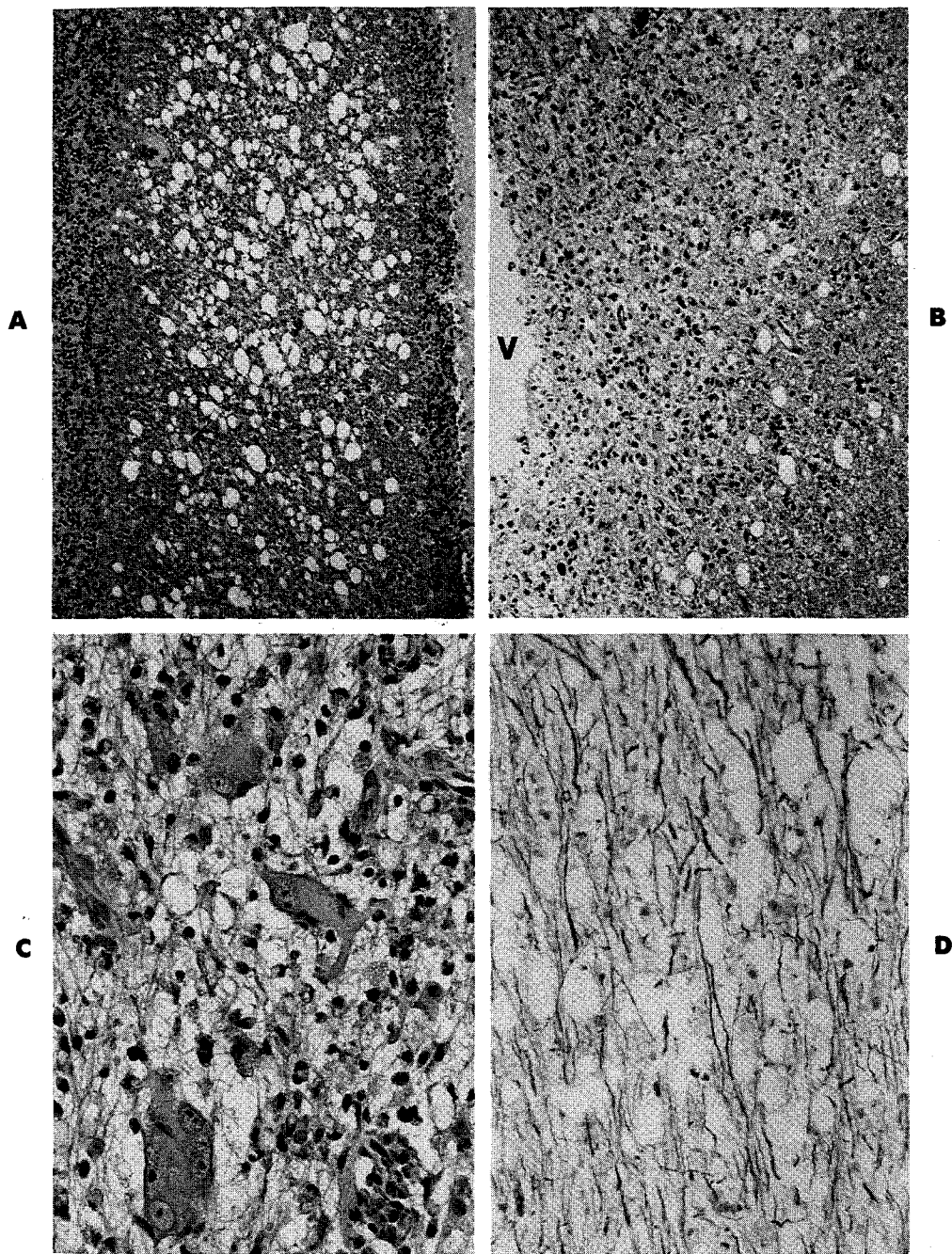


Fig. 3-8. Canine distemper encephalitis. White matter lesions. **A**, Characteristic spongy white matter change, cerebellum. (H&E, $\times 140$.) **B**, Myelin loss and gliosis adjacent to the fourth ventricle (v). (H&E, $\times 140$.) **C**, Hypertrophic and multinucleated astrocytes in rarified white matter lesion. (H&E, $\times 350$.) **D**, Silver impregnation of axons, which are largely preserved in early lesions. (Holmes, $\times 350$.)

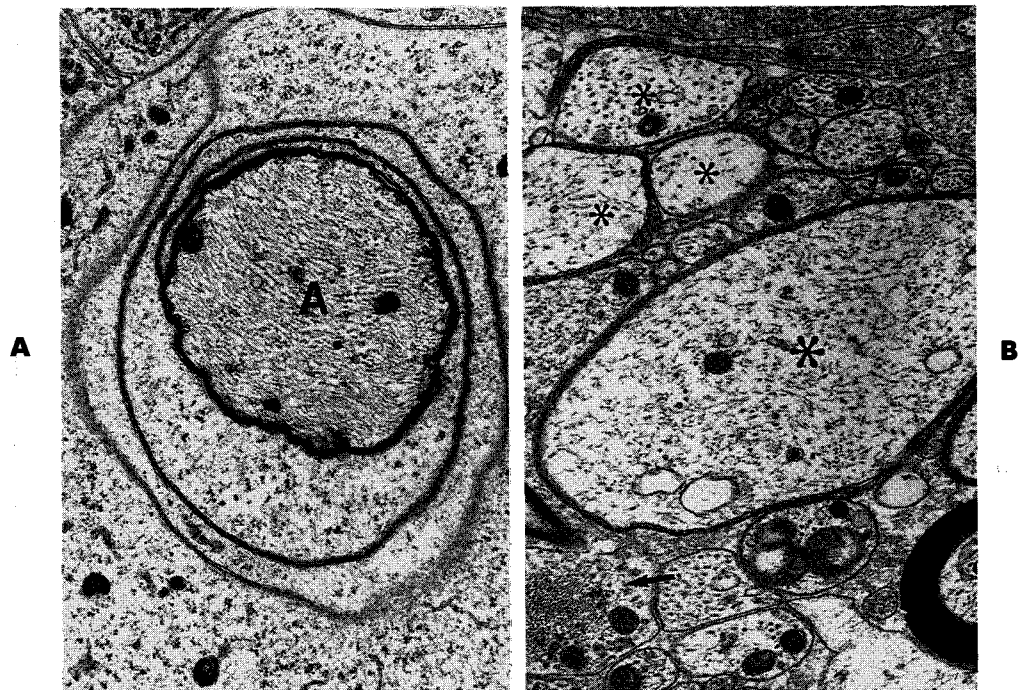


Fig. 3-9. Canine distemper encephalitis. Electron microscopy. **A**, Processes of a macrophage spiral around the central axon (A), stripping myelin lamellae. ($\times 15,600$.) **B**, Several axons (asterisks) are largely or totally demyelinated. Arrow indicates astroglial process with cytofilaments. ($\times 24,750$.)

lin sheath it produces. Oligodendrocytes are progressively lost in the areas of white matter injury, but experimental studies have not shown that this is a consequence of viral infection of these cells. It could be argued that infection with CDV produces rapid cytolysis of oligodendrocytes, but this would be unusual because this is not a hallmark of infection with the virulent virus in other glial cells. As mentioned earlier, although oligodendrocyte infection has been documented by EM, it is an uncommon finding. This raises the question whether infection of oligodendrocytes is more common than so far shown and is defective or restricted. In this vein, crucial new studies by Zurbriggen, Yamawaki, and Vandeveld⁶⁵ indicate that in brain cell cultures oligodendrocytes do contain CDV nucleic acid sequences but fail to produce viral proteins. In fact, studies of dissociated canine brain cell cultures infected with CDV provide intriguing parallels to the situation in vivo. Most cell types in culture are readily shown to be susceptible to infection, with the exception of mature oligodendrocytes,^{66,67} in which the infection rate appeared to be only of the order of 2% to 3%.⁶⁸ However, such studies depended on the demonstration of viral antigens to establish infection; in situ hybridization has shown CDV sequences in many oligodendrocytes.⁶⁵ Oligodendrocytes throughout the cultures show a diminished metabolic activity and subsequently

undergo degeneration and necrosis.^{66,68-70} It remains to be established whether this defective infection can account for the demise of these cells in vitro and then, crucially, in vivo. For the cultures, a toxic factor, released by other infected cells, was one hypothetical explanation for the oligodendrocyte degeneration, but this could not be substantiated. An alternative view would be that infected astrocytes fail in their normal function of producing a nutritive or trophic factor needed for oligodendrocyte survival.

Hypothetically, myelin injury might occur indirectly from the deleterious effects of CDV infection on other cells in white matter; astrocytes would be the prime candidate.⁵⁸ Type 2 astrocytes seem to be involved in maintaining integrity at the node of Ranvier,^{71,72} and changes at the node may destabilize the myelin sheath. A second mechanism incriminates the variety of cytokines, such as tumor necrosis factor, that are released by activated astrocytes⁷³ and can produce ballooning myelin injury very similar to that seen in CDE.⁷⁴ Macrophages would also be a source of such mediators.

Evidence for an immune basis to the myelin injury has been sought. Most studies have been unrewarding, especially in the early phase of white matter injury.^{50,75,76} Lymphocyte responsiveness to myelin antigens can be demonstrated in some dogs but does not correlate with the course

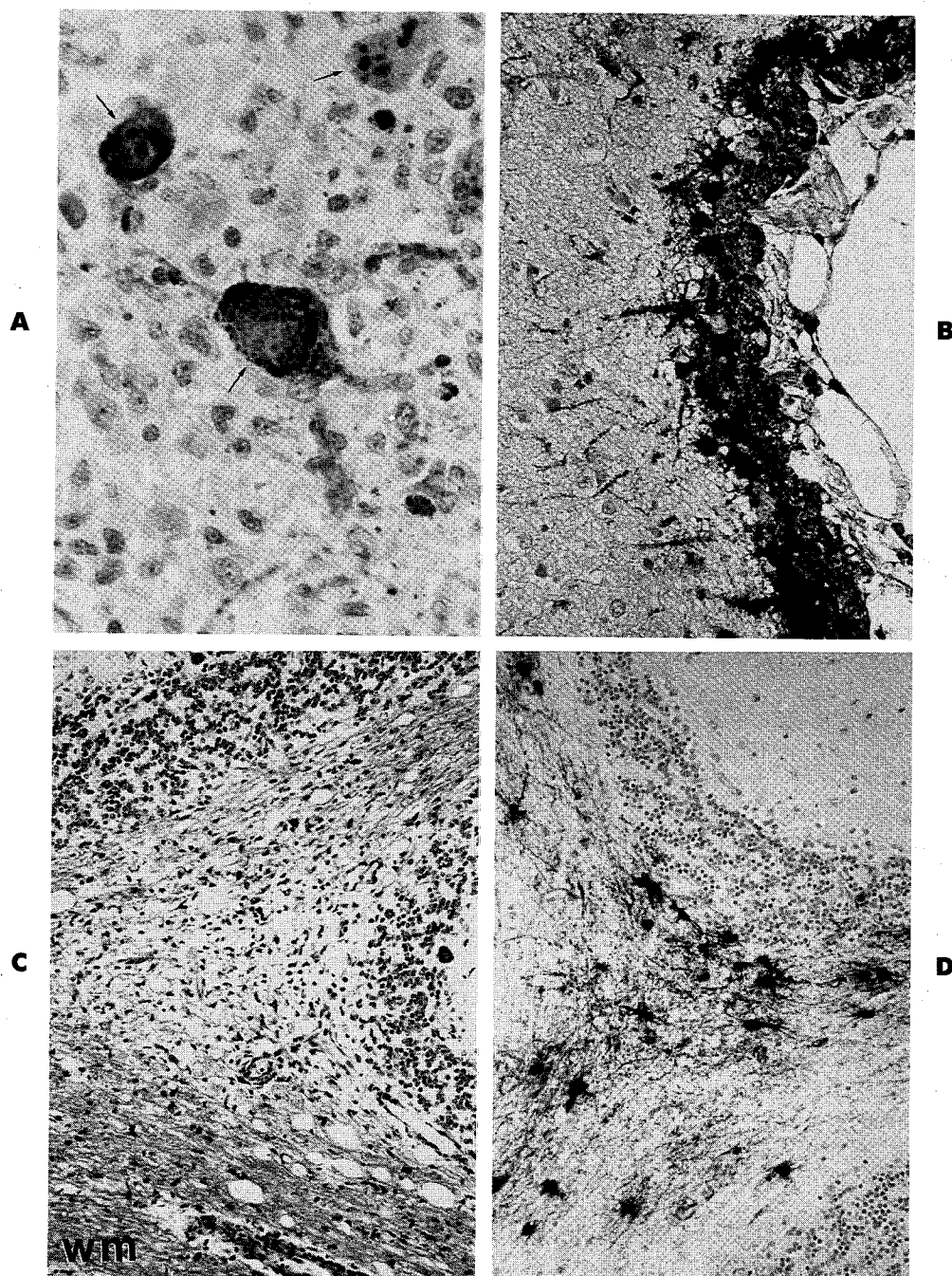


Fig. 3-10. Canine distemper encephalitis. Immunocytochemistry. **A**, Viral antigen in neurons (arrows), medulla. ($\times 715$.) **B**, Viral antigen in astrocytes forming glia limitans, brain stem. ($\times 350$.) **C**, Routine H&E section showing spongy, gliotic lesion adjacent to cerebellar granule cells; normal white matter (*w*m). ($\times 140$.) **D**, Lesion similar to **C** showing virus-positive glial cells. ($\times 180$.)

of the disease or the presence or absence of lesions.⁷⁷ Antimyelin antibodies appear in the serum of dogs with natural or experimental CDV infection, but the titers are highest in recovering dogs that lack CNS changes.⁷⁸ In fact, these cytotoxic antibodies may be directed against a lymphocyte antigen that fortuitously is shared with CNS myelin.⁷⁹ In contrast to an autoimmune reaction, however, evidence for an antibody-dependent immunopathological mechanism of white matter injury, occurring during the inflammatory phase of CDE, has been provided.^{80,81} This scheme involves macrophages that are triggered to release toxic reactive oxygen species following their binding to the Fc receptors of anti-CDV antibody molecules.

Variants of typical CDE will be briefly mentioned. One rare form has become known as **old dog encephalitis** (Cordy's disseminated encephalomyelitis in mature dogs).⁸²⁻⁸⁴ Clinically, these animals are usually depressed, poorly responsive, and sometimes propulsive and have an ataxic gait. Microscopically, the characteristic feature is widespread perivascular cuffing with mononuclear cells (mainly lymphocytes), sometimes forming huge aggregates. Both gray and white matter are affected, particularly in the prosencephalon. There are scattered foci of neuronal degeneration and gliosis with occasional inclusion bodies in neurons and astrocytes. Unlike typical forms of CDE, virus cannot be recovered from the CNS, although viral antigens and nucleocapsids can be demonstrated there, and CSF contains high levels of immunoglobulin.⁸³⁻⁸⁶ Old dog encephalitis may be a persistent infection with a defective virus. In our experience, this form of CDE is exceptionally rare; it must be differentiated from—and perhaps in the past has been equated with—ordinary CDE in mature and old dogs. Another rare variant seen in dogs with CD is **chronic sclerosing leukoencephalitis**,⁸⁷ which is probably an example of very prolonged white matter injury. **Post-vaccinal CDE** develops 1 to 2 weeks after routine vaccination and is manifest by aggressive and violent behavior, progressive ataxia and paresis, recumbency, and death in a few days.^{9,11} Lesions are disseminated but most pronounced in the pontine gray matter and are characterized by malacia, numerous spheroids, and abundant neuronal inclusions (Fig. 3-11). Such episodes are sometimes associated with a particular batch of a multivalent vaccine that includes modified live CDV and are probably due to inadequate attenuation of the CDV component. Subclinical viral infection—for example, with canine parvovirus—may also explain occasional incidents of vaccine induced disease.

References are on page 172.

GRANULOMATOUS MENINGOENCEPHALOMYELITIS

In 1972, Fankhauser et al¹ described their experience with "reticulosis" of the CNS in dogs and, within this syndrome, identified three categories: (1) inflammatory (granuloma-

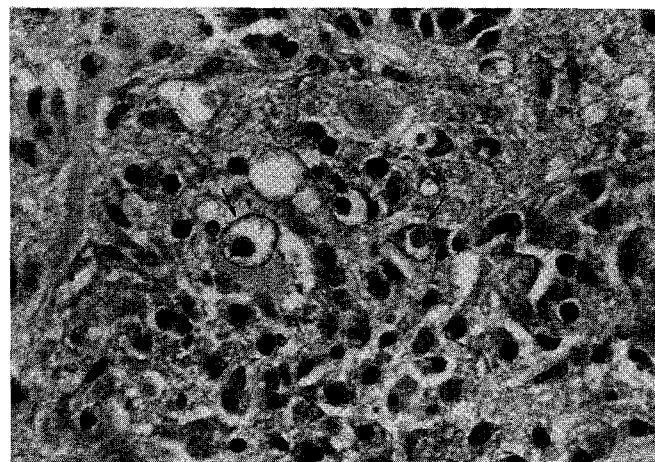


Fig. 3-11. Post-vaccinal canine distemper encephalitis. Gliosis and intranuclear inclusions in two neurons (arrows), medulla. (H&E, $\times 560$.)

toxic) reticulosis, (2) neoplastic reticulosis, and (3) microgliomatosis. The term reticulosis was used to describe proliferations of "reticulohistiocytic" cells, whether derived from the vascular adventitia, from the leptomeninges, or from their counterpart within the CNS parenchyma, the microglial cell. In 1962, Koestner and Zeman² had described primary reticulosis in six dogs, of which several cases were histopathologically similar to those later reported by the Fankhauser group. The distinction between inflammatory and neoplastic reticulosis was usually straightforward: Reticulohistiocytic cells mixed with lymphocytes, plasma cells, and sometimes other leukocytes in the inflammatory form, whereas they predominated in the more monomorphic neoplastic form. Occasional cases, given further study, may have to be reclassified.³

In 1978, Braund et al⁴ described granulomatous meningoencephalomyelitis (GME) in dogs. Although stated to be a condition not documented in the dog, it was noted that the microscopic features of GME were suggestive of inflammatory reticulosis. Furthermore, the authors thought it feasible that (inflammatory) reticulosis and GME were variants of a similar disease process. Despite the fact that differences between reticulosis and GME have been described (for example, in the symmetry and distribution of lesions in the CNS⁵), it is our choice, at this time, to equate GME with what in the literature has previously been referred to as the inflammatory form of reticulosis. Others⁶⁻⁸ seem to concur.

GME is seen in dogs of all ages and breeds. Most cases occur in mature, adult dogs, 1 to 3 years of age, but cases in young puppies and in geriatrics are described. A few breeds have been said to be at increased risk, perhaps miniature Poodles most often,⁹ but no breed appears to be immune. Females are more often affected than male dogs.

Neurological disease usually has an abrupt onset⁴ and an inexorably progressive course,¹⁰ either slowly or rapidly; accordingly, the clinical course may range from several days to a few months. Initially, corticosteroids may afford considerable relief. Clinical signs are variable, reflecting the site of lesions in the neuraxis. Deficits referable to the caudal brain stem and cervical spinal cord are most common and include facial paralysis, circling, head tilt, nystagmus, and, quite commonly, cervical pain.^{4,11} Neurological examination may indicate focal or multifocal disease, and canine distemper encephalomyelitis often has to be considered in the differential diagnosis. A few dogs are pyrexemic and have a leukocytosis.¹⁰ A related form is primarily localized in the optic nerves and optic chiasm. This optic neuritis causes blindness with abnormal pupillary light reflexes.^{12,13}

Examination of CSF is usually rewarding, with an impressive elevation of protein level and a marked pleocytosis.¹⁴ Lymphocytes and plasma cells predominate, with fewer monocytes and a sprinkling of polymorphonuclear cells.

At necropsy, gross lesions are evident if the angiocentric inflammatory reaction is sufficient to produce a mass effect. Lesions predominate in white matter, particularly of the cerebellomedullary region, and are seen as areas of swelling and yellow to gray discoloration (Fig. 3-12, A) with obliteration of normal structure. On occasion, dogs present with a syndrome of optic neuritis and at postmortem examination have grossly swollen optic nerves.¹² Lesions may occur focally in the CNS but more commonly are widely disseminated. One case we encountered¹⁵ presented as a cerebellar mass but after sectioning was found to have multifocal, smaller lesions throughout the neuraxis. Microscopically, the hallmark of GME is a unique pattern of inflammatory cell accumulation and/or proliferation around blood vessels (Fig. 3-12, B and C). Sometimes cells are arranged in a whorled pattern around the central vessel,⁹ a feature that is emphasized by reticulin stains. These cells in the perivascular compartment consist of varying proportions of lymphocytes, plasma cells, large mononuclear cells, and infrequently, neutrophils. In the early papers, the large mononuclear cells were given many designations including reticuloendothelial cells, reticulohistiocytes, perithelial cells, histiocytes, and macrophages. A characteristic feature of GME, seen in some cases, is an epithelioid differentiation of this histiocytic component, such cells often forming a discrete nest within the cuff. Infiltration of all these cells into the CNS parenchyma is typically minimal; however, as the perivascular population around several vessels expands and coalesces, the intervening parenchyma is progressively compressed and obliterated, and it is such cases that are grossly evident at necropsy. The surrounding neuropil shows a modest astrogliosis, which may be more striking in neighboring areas affected only by chronic edema. Leptomeningeal involvement is consistent and may be widespread.

Clinically and pathologically, GME must be differentiated from CDE and other causes of granulomatous encephalomyelitis (fungal, protozoan, and the like) in the dog. In GME, macrophages often contain PAS-positive material,¹⁰ but this may be simply tissue debris. Nothing has been published on the ultrastructural features of this disease, probably not so much from the lack of looking as rather a failure to observe anything worth reporting.

The cause of GME is not known. Both rabies and canine distemper have been suggested as possible causes, presumably as expressions of atypical infection with these viruses. However, GME occurs in rabies-free countries such as Australia. Involvement of CDV seems unlikely insofar as our clinical impression is that, with the marked reduction in the incidence of CD due to vaccination, GME has become relatively more common and important. Attempts to demonstrate CDV antigen in cases of GME have been unsuccessful.^{15,16} A purely speculative hypothesis would be that GME is caused by a retrovirus, perhaps contaminating (and thus spread by) canine vaccines, akin to avian reticuloendotheliosis.

In other animal species, inflammatory CNS lesions of this type (unrelated to recognized infectious agents) are quite uncommon. We have encountered sporadic cases of inflammatory reticulosis/granulomatous meningoencephalitis in the horse, usually presenting as disseminated mass lesions in the brain (Fig. 3-13).

The neoplastic form of reticulosis¹ was defined as a monomorphic variant in which the "reticulohistiocytic" cell was dominant, often with prominent mitotic figures. Such cases are much less common than is the inflammatory form of reticulosis (GME). Neoplastic reticuloses and related tumors, such as those previously designated as reticulum-cell sarcoma and microgliomatosis, are currently viewed in humans as being B-cell lymphomas,¹⁷⁻¹⁹ although a neuroectodermal origin for microgliomatosis has occasionally been proposed.²⁰ This area is discussed in the chapter on CNS tumors.

References are on page 174.

PUG DOG ENCEPHALITIS

A unique, chronic, nonsuppurative meningoencephalitis occurs in juvenile to young adult male and female Pug dogs.¹ The disease has been observed in Pugs from several states² and in Australia, New Zealand, Japan,³ and Switzerland. The onset of clinical disease varies from 6 months to 7 years of age but tends to the earlier part of the range; three littermates, affected between 9 and 19 months of age, have been seen at Cornell. Lesions are predominantly in the cerebral hemispheres, and the clinical signs observed reflect this distribution. Most dogs have generalized seizures, depression, circling, and visual defects. Some die after only a few days of signs, whereas others have had seizures for up to 6 months before death or euthanasia. Ataxia and pa-

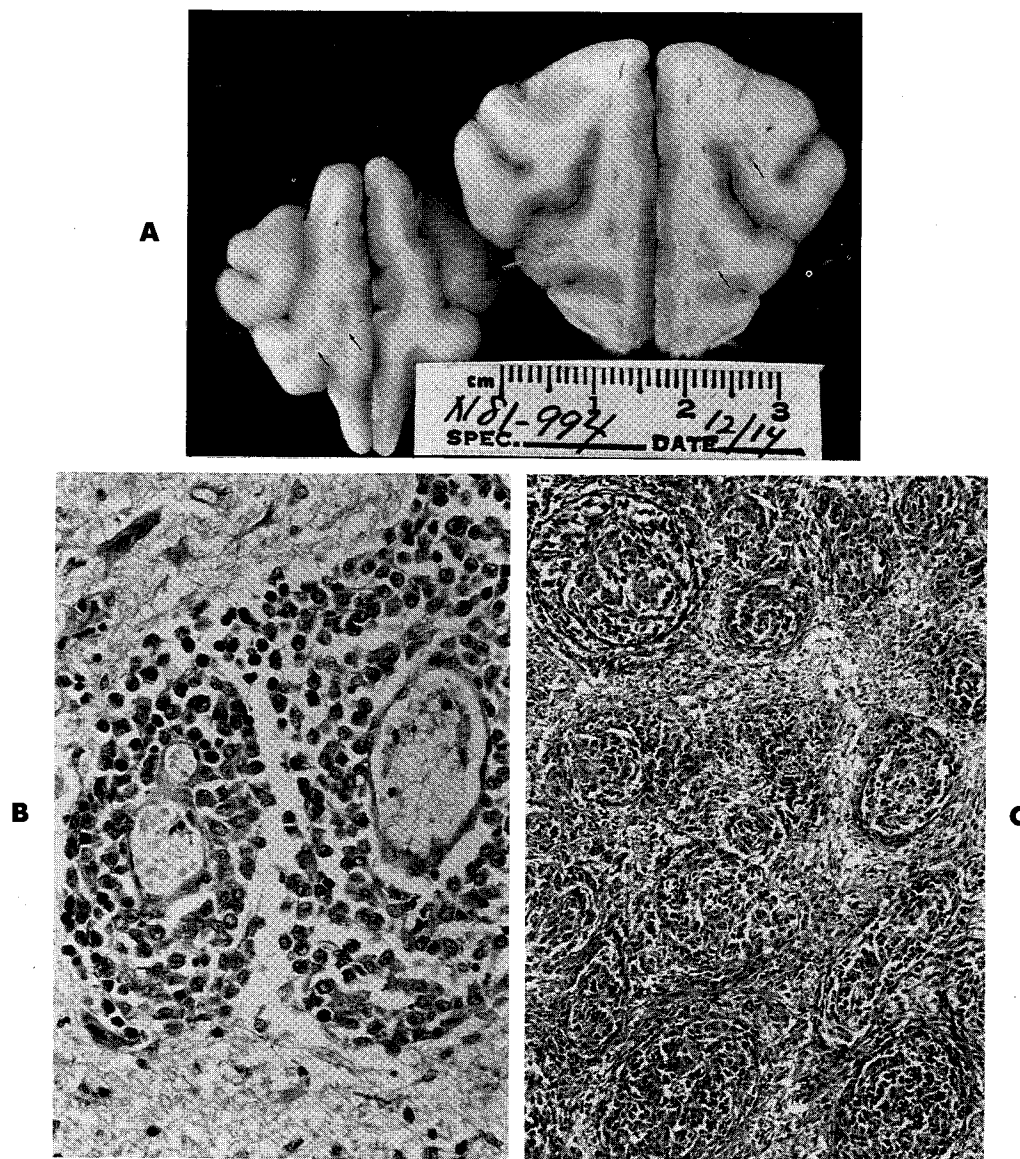


Fig. 3-12. Granulomatous meningoencephalitis, dog. **A**, Gross lesions (discolored plaques) in frontal lobe white matter (*arrows*). **B**, Two vessels with perivascular cuffs of macrophages, plasma cells, and lymphocytes in the medulla. (PAS, ×350.) **C**, Multiple confluent perivascular cuffs, cerebellum. The intervening neural tissue is degenerate. (H&E, ×140.)

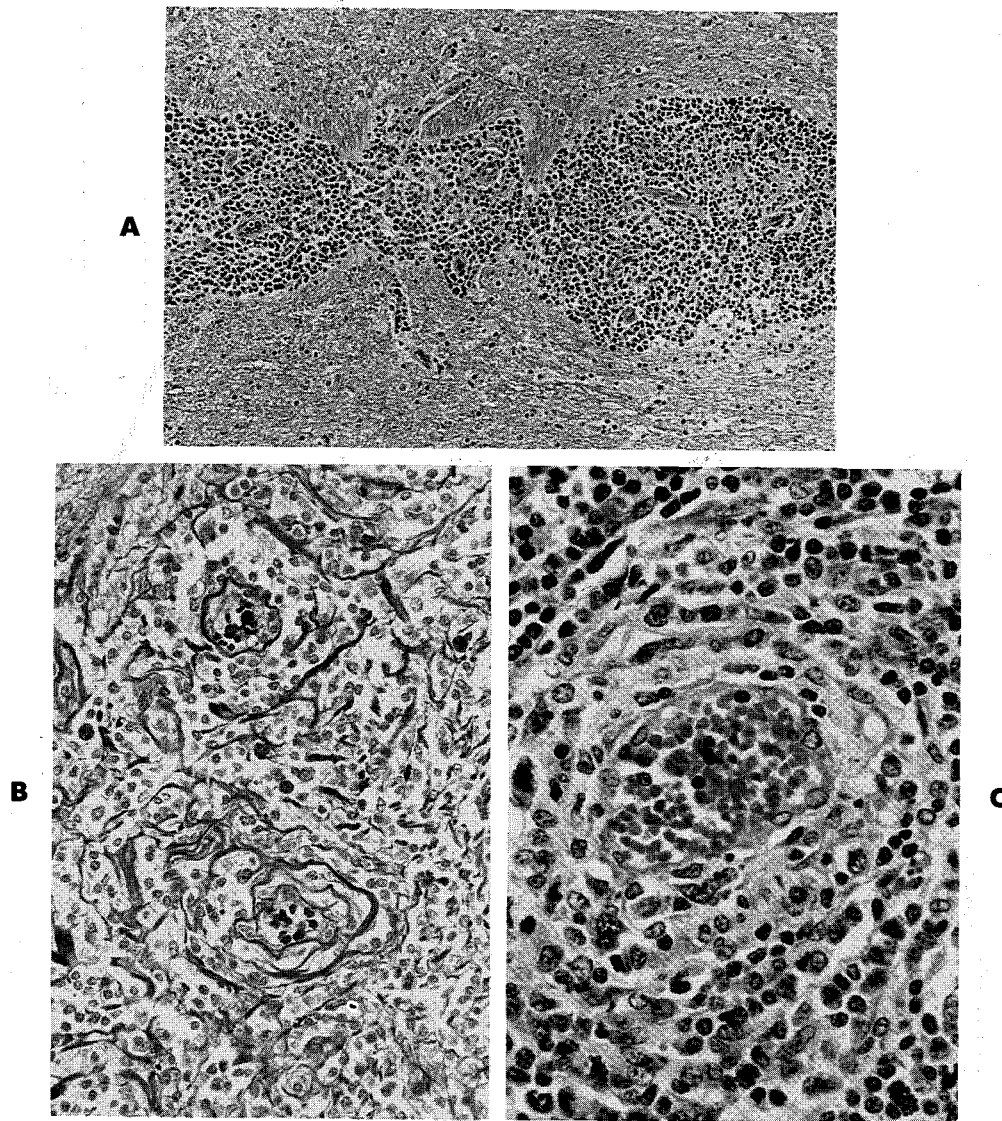


Fig. 3-13. Granulomatous meningoencephalitis, horse. **A**, Coalescing perivascular cuffs, cerebrum. (H&E, $\times 140$.) **B**, Perivascular reticulin deposition in cerebral GME lesion. (Gomori's reticulin, $\times 350$.) **C**, Detail of mixed cell population in equine GME. (H&E, $\times 560$.)

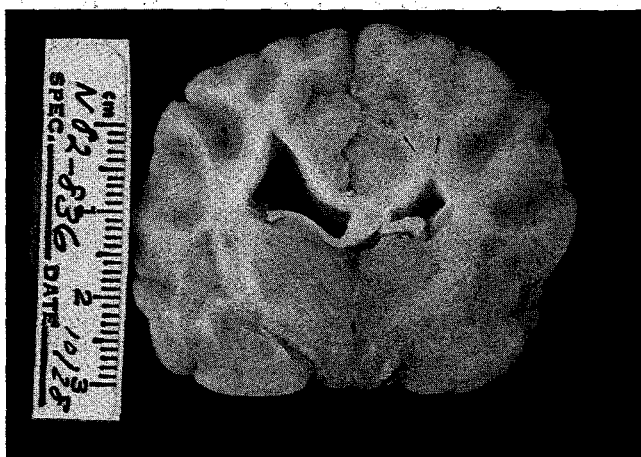


Fig. 3-14. Pug dog encephalitis. Cavitation in corona radiata (arrows) and loss of normal gray-white junction (compare with other side), cerebrum.

resis, reflecting brain stem, cerebellar, and/or spinal cord involvement, are much less common. CSF examination reveals a lymphocytic pleocytosis.¹

At necropsy, the gyri of the cerebral hemispheres may appear slightly flattened. Transverse sections of the cerebrum reveal gross lesions that usually are asymmetrical. Areas in the centrum semiovale and corona radiata are somewhat sunken and grayish, with a loss of the normal distinction between gray and white matter (Fig. 3-14). Sometimes such areas are cavitated, whereas in other cases the affected area appears swollen. Less consistently, yellowish areas of cerebrocortical necrosis are evident. Microscopically, there is a severe necrotizing meningoencephalitis involving the cortical leptomeninges, gray and white matter (Fig. 3-15). Inflammation and tissue necrosis are perhaps most severe in the white matter, accounting for the macroscopic changes that can be found. In such areas, the parenchyma is rarefied and flooded with perivascular and parenchymal infiltrates of lymphocytes, plasma cells, and histiocytes; many mononuclear cells have small, round, dense nuclei and are difficult to identify. Reactive astrogliosis is extensive. Multifocal inflammatory changes in the cerebral cortex are also found, sometimes superimposed upon areas of laminar cortical necrosis, although some areas of ischemic neuronal change occur without concurrent inflammation. This neuronal loss may be primary or a consequence of chronic seizure activity. In both white and gray matter, areas of cribriform change or frank cavitation can be found. Leptomeningitis is most severe in the sulci and may overlie unaffected gray matter.

Lesions in the brain stem, cerebellum, and spinal cord are milder and less common. Two of three trigeminal ganglia examined had a ganglionitis.¹ Very preliminary electron mi-

croscopic studies of white matter lesions from one Pug have shown extensive degeneration amid a mononuclear cell influx within which plasma cells were conspicuous. Multifocal myocardial necrosis is occasionally seen in animals following a variety of CNS insults⁴ and has been recorded in Pug dog encephalitis.⁵

The cause of Pug dog encephalitis is unknown. Virus isolation was attempted in two of our cases and was negative. Microscopically, the lesions have been confused with granulomatous meningoencephalitis (GME) but, unlike GME, are less purely angiocentric, involve both gray and white matter, and predominate in the cerebrum. We have viewed this as a novel disorder of the Pug breed, but a clinically and pathologically similar necrotizing encephalitis has been seen in Maltese dogs in the United States and Australia.⁶ In contrast to the Pug and Maltese dog disorders, a necrotizing encephalitis with consistent brain stem involvement has been described in Yorkshire terriers.⁷

References are on page 174.

IDIOPATHIC IMMUNE-MEDIATED POLYARTERITIS AND MENINGOENCEPHALOMYELITIS

Polyarteritis is a hallmark of the immune-mediated diseases such as systemic lupus erythematosus and rheumatoid arthritis. In the dog, and particularly in Beagles, polyarteritis is sporadically encountered as a separate and distinct syndrome that has been recognized for some time.¹ Arterial lesions may be found in many organs, most frequently the heart² and the CNS. Because the clinical signs are commonly a consequence of spinal leptomeningeal vasculitis,³ we have designated this clinical variant **canine meningeal polyarteritis**. Indeed, pure coronary vessel arteritis may be subclinical.²

Beagle dogs, frequently laboratory-bred experimental animals, are commonly affected, and there are sporadic reports in other breeds.^{4,5} Because dogs with this disorder experience severe pain, the condition has also become known as **Beagle pain syndrome**. Dogs are affected at approximately 6 to 9 months of age and are of either sex.⁶ They present with fever, depression, and a hunched posture with profound guarding of the head and neck, mimicking an acute cervical intervertebral disk protrusion. Manipulation almost anywhere on the body elicits severe pain. Affected dogs may spontaneously improve in a few days to weeks, sometimes to relapse with subsequent episodes of pain, depression, and fever. An identical clinical syndrome is encountered in veterinary practice, usually in middle-sized to large dogs less than 2 years old.^{7,8}

Dogs with clinical signs have neutrophilia, and the CSF, which may be blood-tinged, is remarkable for the high elevation of cells,^{7,9} most of which are polymorphonuclear. The CSF also contains excessive protein and erythrocytes, some of which are undergoing phagocytosis by leukocytes.

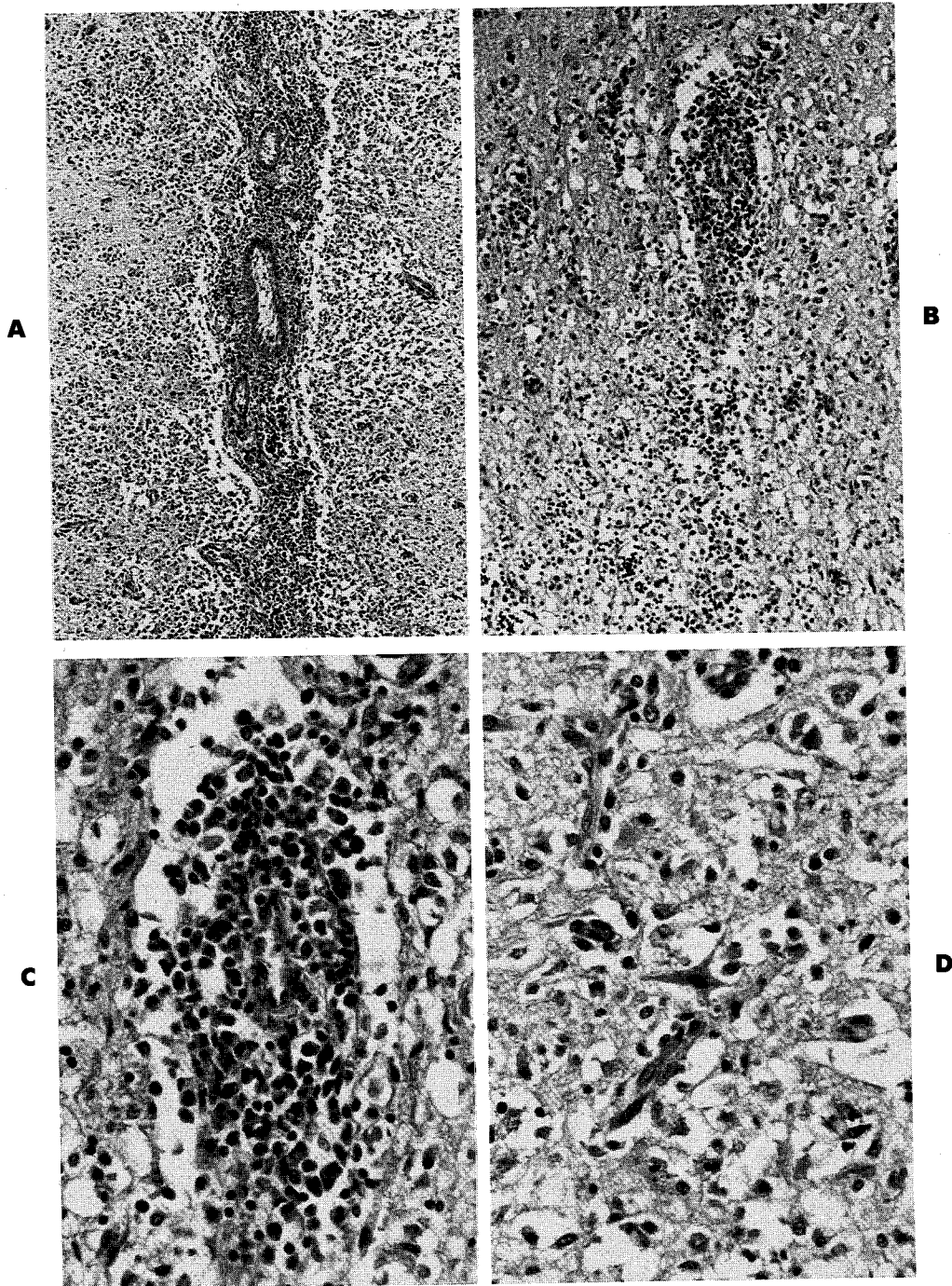


Fig. 3-15. Pug dog encephalitis. **A**, Dense, nonsuppurative meningitis and infiltration of the adjacent cerebral cortices. (H&E, $\times 90$.) **B**, Perivascular cuff in cerebral white matter with infiltration into neighboring rarefied tissue. (H&E, $\times 140$.) **C**, Detail of perivascular cuff in **B**. Plasma cells are abundant. (H&E, $\times 350$.) **D**, Neuronal necrosis in Pug dog encephalitis, cerebrum. Central ischemic neuron. (H&E, $\times 350$.)

The CSF findings may suggest bacterial meningitis, but the neutrophils neither show toxic changes nor contain bacteria, and aerobic cultures are sterile. Peripheral blood B lymphocyte numbers are increased, whereas T cells are diminished.¹⁰ Lymphocyte blastogenic responses are depressed during and between episodes of illness.¹¹ Direct Coomb's, antinuclear antibody, and rheumatoid factor tests have been negative;^{5,7,11} although a few dogs have had positive LE clot tests,⁷ this result alone is of limited specificity.

At necropsy, severe subarachnoid hemorrhages extend over the entire length of the spinal cord and brain stem. Microscopic findings are a severe necrotizing arteritis of leptomeningeal arteries with an associated leptomeningitis (Fig. 3-16). Lesions are found along the entire spinal cord and caudal brain stem; more rostrally in the brain, the reaction is mostly a mild leptomeningitis. Involvement of intramedullary arteries and of the neuroparenchyma is remarkably modest. Affected arteries show fibrinoid necrosis of the tunica media, degeneration of the surface endothelium, and a transmural infiltrate of neutrophils, lymphocytes, plasma cells, and macrophages. These cells, admixed with fibrin, extend into the adjacent subarachnoid space, the sheath of nerve rootlets, and dura. Lesser affected vessels have only an adventitial infiltrate. Occasionally, vessels show acute thrombosis or fibrous organization of thrombi. Clusters of hemosiderin-laden macrophages attest to previous episodes of leptomeningeal hemorrhage.

Canine meningeal polyarteritis has the pathological features of an immune-mediated vasculitis. Affected Beagle dogs sometimes have a concurrent lymphocytic thyroiditis,⁹ a further immunopathological disorder to which this breed is predisposed. Attempts to demonstrate immunoglobulin deposits within vascular lesions in the heart or CNS have been unsuccessful,^{2,9,12} as has been our experience. In a review of this syndrome, it was suggested that the stress of experimental manipulation in laboratory dogs may be involved in precipitating the disorder.¹³ Clinical experience has shown a dramatic response to corticosteroid therapy;⁷ antibiotics afford no evidence of relief.

A **mesangiocapillary glomerulonephritis** occurs in young **Finnish Landrace lambs**. Affected animals are found dead or have a short course of neurological disorder, manifest by apparent disorientation, walking in circles, nystagmus, and seizures.¹⁴⁻¹⁶ Clinically affected lambs have palpably enlarged and tender kidneys. Histopathological examination reveals a mesangiocapillary glomerulonephritis with immunoglobulin and complement deposits within the glomeruli. In many affected lambs, there are changes in the choroid plexuses, most remarkably edema of the plexus stroma and immunoglobulin deposits.¹⁶ Less commonly, a spongy change is found in the cerebral hemispheres at the gray-white matter junction.

Quantification of serum complement from newborn Finnish Landrace lambs has revealed a severe deficiency of the third component of complement.¹⁷ It is perhaps paradoxical



Fig. 3-16. Canine meningeal polyarteritis. Fibrinoid necrosis in a spinal cord leptomeningeal arteriole. (H&E, $\times 350$.)

that these hypocomplementemic lambs develop immune-complex disease in their glomerular and choroid plexus vasculature. Presumably this occurs because complement has important opsonizing properties, allowing fixed tissue macrophages to remove immune complexes and for the solubilization of other complexes deposited in tissue. The neurological disorder may have a dual basis,¹⁶ namely, altered choroid plexus function and the effects on the CNS of renal failure (so-called renal or uremic encephalopathy¹⁸).

Documentation of this syndrome in sheep raises the question whether a comparable situation exists in dogs with **systemic lupus erythematosus (SLE)**. Ophthalmological and neurological-psychiatric disorders in SLE are well recognized in humans,^{19,20} and neuropathies have been reported less frequently. Immune complex disease in canine SLE is seen predominantly as polyarthritis, glomerulonephritis, dermatologic disease, anemia, and thrombocytopenia. However, behavioral changes, often accompanied by seizures, have been noted in the dog,²¹ but studies of the CNS in this disease have not been reported. In murine SLE, neurological abnormalities and CNS inflammation have been detected.^{22,23} In young **Akita dogs with polyarthritis**,²⁴ a disorder similar to human juvenile rheumatoid arthritis, meningitis or meningoencephalitis has been demonstrated from analysis of CSF or at necropsy.

Immune complex formation is probably important in the pathogenesis of **feline infectious peritonitis** and **equine infectious anemia**. Other immunopathological mechanisms

of tissue injury are believed to be operative in **visna**, **caprine arthritis encephalitis syndrome**, **malignant catarrhal fever**, and **Theiler's encephalomyelitis in mice**. All these diseases are discussed elsewhere in this chapter.

References are on page 174.

CANINE HERPESVIRUS ENCEPHALOMYELITIS

Canine herpesvirus (CHV) causes an acute, disseminated, necrotizing infection, usually in puppies younger than 3 weeks of age. Multifocal necrosis occurs in the liver, kidneys, lungs, and other organs.¹ Occasional parenchymal cells in these organs contain eosinophilic intranuclear viral inclusions. Affected puppies have a nonsuppurative meningoencephalitis (Fig. 3-17), most severe in the brain stem and cerebellum. Necrosis and inflammation involve gray and white matter, particularly the former.² Mononuclear cell infiltrates are accompanied by vascular endothelial hypertrophy and hyperplasia. Cerebellar cortical necrosis is observed with some consistency,^{2,3} sometimes involving the entire width of the folium. Puppies surviving the acute disease may have cerebellar (and retinal) dysplasia.⁴ Polyneuritis and a ganglionitis involving craniospinal and sympathetic ganglia may also be observed.⁵

Beyond 3 weeks of age, CHV appears to be a self-limiting infection; even by just 6 weeks, puppies are quite resistant to experimental infection.⁶ Immunity probably lasts for life⁷ and may be associated with persistent, subclinical infection.

References are on page 175.

CANINE ADENOVIRUS CNS VASCULITIS

Canine adenovirus type 1 is the cause of infectious canine hepatitis. On very rare occasions, infection is peracute, and affected dogs may simply be found dead. At postmortem examination, multiple remarkably severe hemorrhages are found in the brain involving the brain stem and caudate nuclei. The cerebral and cerebellar cortices are spared. Microscopic findings are of disseminated fresh hemorrhages in the neuropil. Capillaries and venules are prominent due to an infiltration in and about their walls with mononuclear inflammatory cells (Fig. 3-18, A), which may be admixed with erythrocytes and a little fibrin. Infiltrates of inflammatory cells spilling into the parenchyma and significant gliosis are lacking. Pathognomonic findings are intranuclear amphophilic inclusions in vascular endothelial cells.

This pattern of CNS adenovirus-induced vasculitis has been described in **foxes**, where it is designated fox encephalitis,^{1,2} and **coyotes**,³ and perhaps it occurs sporadically in other species (Fig. 3-18, B).

References are on page 175.

PARAINFLUENZA AND NEWCASTLE DISEASE ENCEPHALOMYELITIS

The genus *Paramyxovirus*, within the family Paramyxoviridae, includes the parainfluenza viruses, mumps, and Newcastle disease virus. Parainfluenza viruses are pathogens

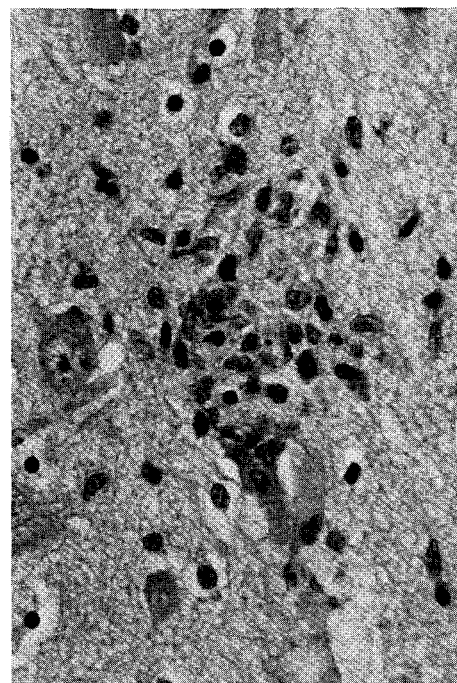


Fig. 3-17. Canine herpesvirus encephalitis. Microglial nodule, thalamus. (H&E, $\times 560$.)

of the respiratory tract in many species. **Canine parainfluenza virus (CPIV)** is one of the etiological factors in the syndrome of "kennel cough," a tracheobronchitis of the dog. In young puppies, intracerebral inoculation with CPIV induces an acute, necrotizing encephalitis. Hydrocephalus of the lateral and third ventricles occurs in many of the survivors.¹ Viral antigen is demonstrable in ependymal cells during the acute stage of the infection. Ultrastructural studies show degeneration in ependymal cells during the acute stage, with dysplastic changes in chronically affected (hydrocephalic) dogs.² Aqueductal stenosis and the most severe hydrocephalus occur in puppies inoculated as neonates, suggesting that the developing brain may be at greatest risk early in life. Johnson and Johnson³ have shown a similar capacity for mumps virus to induce hydrocephalus in newborn hamsters. Interestingly, the healed stenotic aqueduct had all the features of a primary malformation.⁴ Whether CPIV can cross the placenta and infect the developing canine fetus or can invade the developing CNS postnatally is still to be established. Thus at this time, the importance of CPIV as a cause of spontaneous encephalitis and hydrocephalus in the dog is unknown.

Although a spontaneous, periventricular, necrotizing encephalitis associated with hydrocephalus has been described in the dog, the etiology remains to be established. Clinically and pathologically, experimental CPIV infection differs from this hydrocephalus with periventricular encephalitis in dogs.⁵

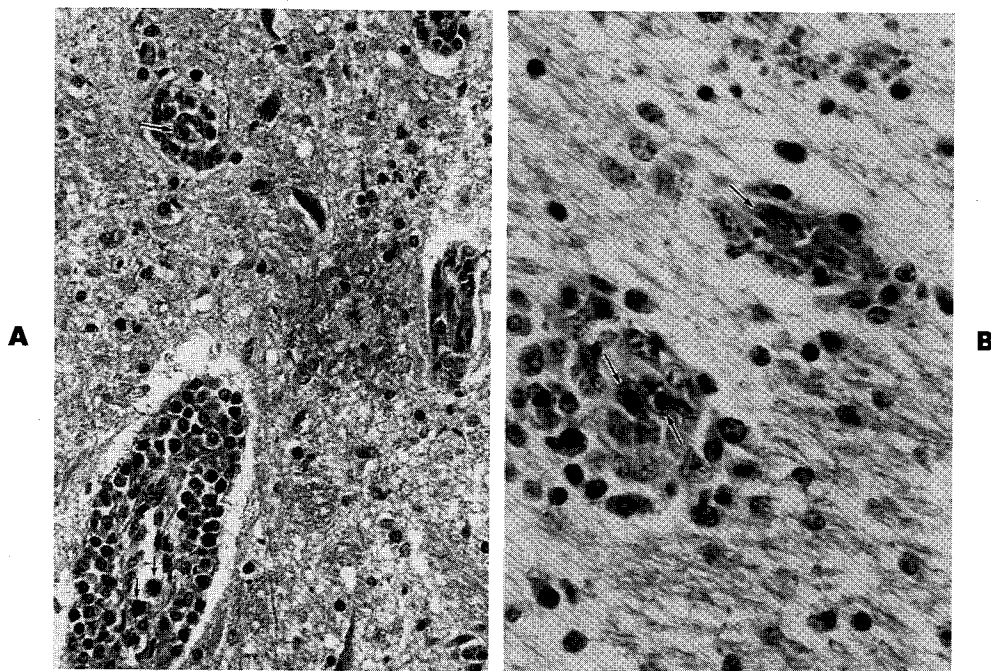


Fig. 3-18. A, Canine adenovirus vasculitis. Endothelial intranuclear inclusions (*arrows*) and vasculitis, midbrain. (H&E, $\times 350$.) B, Putative adenovirus vasculitis, cow. Endothelial intranuclear inclusions (*arrows*) and vasculitis, hippocampus. (H&E, $\times 560$.)

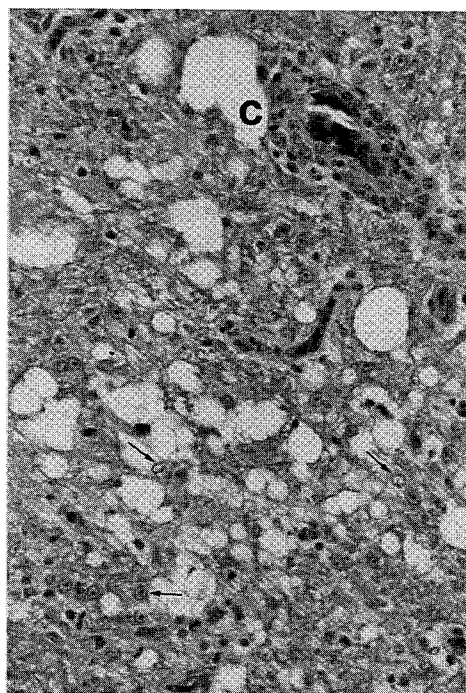


Fig. 3-19. Newcastle disease, chicken. Lymphocytic perivascular cuffing (*c*); vacuolar white matter injury and astrogliosis (*arrows*). (H&E, $\times 350$.)

Munday and colleagues⁶ described an ataxic, day-old, **Aberdeen-Angus calf** in which intracytoplasmic inclusion bodies were found in most large neurons of the brain and spinal cord. Ultrastructurally, these bodies contained filamentous structures resembling paramyxoviral nucleocapsids, and, on serological grounds, parainfluenza type 3 infection was proposed.

Newcastle disease is a potentially important pathogen in **chickens**.⁷ Viral strains vary in their virulence; accordingly, infection may range from inapparent to that resulting in extensive mortalities. A wide range of birds and even rodents may be infected. In chickens, turkeys, and other birds, there is systemic infection with signs of respiratory, intestinal, and CNS disease. Microscopic lesions in the neuraxis are a nonsuppurative encephalomyelitis (Fig. 3-19) with mononuclear cell perivascular cuffing, focal gliosis, and neuronophagia.^{8,9} A strain of Newcastle disease virus has more recently been associated with infection and clinical disease (often neurological) in **pigeons**.¹⁰

References are on page 175.

MENINGOENCEPHALOMYELITIS IN POINTER DOGS

Braund^{1,2} has identified a **pyogranulomatous meningoencephalomyelitis** of mature Pointer dogs. Affected animals show neck rigidity, a lowered head carriage, and reluctance to move, signs suggesting neck pain probably from meningitis. CSF examination reveals a remarkable pleo-

cytosis (to 1000 leukocytes/dl, mainly neutrophils) and elevated protein levels. Neuropathological findings are diffuse but most pronounced at the caudal brain stem–cervical spinal cord region. A mixed neutrophilic and lymphoplasmacytic inflammation involves the leptomeninges and parenchyma of the brain and spinal cord. In some cases, necrosis of gray matter in the spinal cord is found; this is believed to be secondary to the meningitis and associated vascular damage. Attempts to identify the causative agent have been unsuccessful.

References are on page 175.

FELINE INFECTIOUS PERITONITIS

Feline infectious peritonitis (FIP) is a systemic infection of domestic and occasionally other felines, caused by a corona virus. There is compelling evidence that tissue injury and clinical disease are immune-mediated^{1,2} and probably occur in only a small proportion of exposed animals.

Two clinically distinct forms of FIP are recognized. One results in massive abdominal distension with proteinaceous fluid, and the disease was so named for this pattern. Our concern here is with the “brain and eye” form of FIP in which fluid effusions in body cavities are minimal.

The neurological form of FIP can probably occur at any age; we have described a case that was lethal by 12 weeks of age in a kitten.³ Clinical signs include general evidence of malaise such as anorexia, weight loss, and fever. Central nervous system signs are variable,⁴ as involvement of the CNS may be diffuse, multifocal, or localized. Signs referable to cerebellomedullary involvement including spastic paresis, ataxia, nystagmus, and balance loss are most common in our experience. Occasionally cats show only slowly progressive signs of thoracolumbar or cervical spinal cord disease. FIP meningoencephalitis is the most common inflammatory disorder of the feline neuraxis that we encounter.

At necropsy, gross lesions are usually present, but they may be subtle. Evidence of gross brain swelling is infrequent. Meningeal opacity may be evident around the medulla and choroid plexuses of the fourth ventricle. Transverse sections of the brain (Fig. 3-20) show mild to marked thickening of all choroid plexuses, which are sometimes coated with a white tenacious exudate. The surfaces of the ventricles are frequently roughened and irregular and may have a slight brownish discoloration. Ependymal cells may be totally lost and replaced by a coat of fibrin. Sometimes this protein-rich exudate coagulates within the ventricles in the preserved brain. The inflammatory ependymal lesion in the aqueduct may prevent CSF flow, causing ventricular dilation rostral to it. This same lesion in the central canal can lead to hydromyelia at all levels of the spinal cord by destruction of the ependymal surface. Hydromyelia may also follow as a result of increased intraventricular pressure.⁵

Microscopic examination reveals a severe pyogranulomatous leptomeningitis, choroiditis, ependymitis, and encephalomyelitis (Fig. 3-21). The inflammatory process is clearly

focused at the inner and outer surfaces of the CNS,⁶ with only secondary extension into the neuroparenchyma. Any such extension is more severe from the ependymal than the meningeal surfaces. Recognition of this surface-related pattern can be helpful in differentiating FIP from other forms of encephalomyelitis in the cat.

The nature and composition of the microscopic lesions is somewhat variable. Tissue necrosis and fibrin exudation may be severe or mild. The leukocytic influx is typically mixed with lymphocytes, many plasma cells (including some with Russell bodies), and macrophages. Polymorphonuclear cells may be encountered in low numbers or in profusion, perhaps depending upon the stage of the disease. A CSF examination in clinical cases of FIP often reveals markedly elevated proteins and extensive pleocytosis; the latter may be predominantly mononuclear or mixed mononuclear and polymorphonuclear. Serum immunoglobulin levels are often elevated in these cats.

The surface inflammatory reaction is blood vessel-related, particularly with respect to venules. Periphlebitis and phlebitis are less frequently encountered than in FIP lesions of the visceral organs (e.g., the kidneys), but PAS stains often reveal fibrinoid vascular degeneration. Many cats with the CNS form of this disease also have a severe panophthalmitis, particularly involving the anterior uvea.

The pathogenesis of FIP is believed to involve immunopathological mechanisms. Viral antibodies are not neutralizing and, if passively transferred to naive kittens, prior to infection, will result in more acute and fulminating disease. Immune-complex^{7,8} and perhaps also cell-mediated mechanisms of hypersensitivity are likely to be operative.

References are on page 175.

FELINE POLIOENCEPHALOMYELITIS

Nonsuppurative encephalomyelitis in the cat caused by rabies and pseudorabies viruses is well documented. It seems probable that on occasion other feline viral agents may invade the CNS, for example, felid herpesvirus 1, which can persist latently in the trigeminal ganglion.¹ There is in the cat a syndrome of polioencephalomyelitis that neuropathologically resembles enterovirus infections such as Teschen-Talfan disease of swine. The cause of this feline disease is not known, but the tissue reaction has all the hallmarks of a neurotropic viral agent. The syndrome is sporadic but has been observed worldwide in cats of all ages. Affected animals have a subacute to chronic course of neurological disease manifested mainly as paresis and ataxia of pelvic or all four limbs. Behavioral changes, seizures, and nystagmus are seen in some cases.

At necropsy, there is a disseminated meningoencephalomyelitis (Fig. 3-22) that is most severe in the brain stem and spinal cord. Lesions show a predilection for gray matter and are characterized by neuronal degeneration, neuronophagia, focal gliosis, and perivascular cuffs of lymphocytes and plasma cells. Degenerative changes in the ventral gray

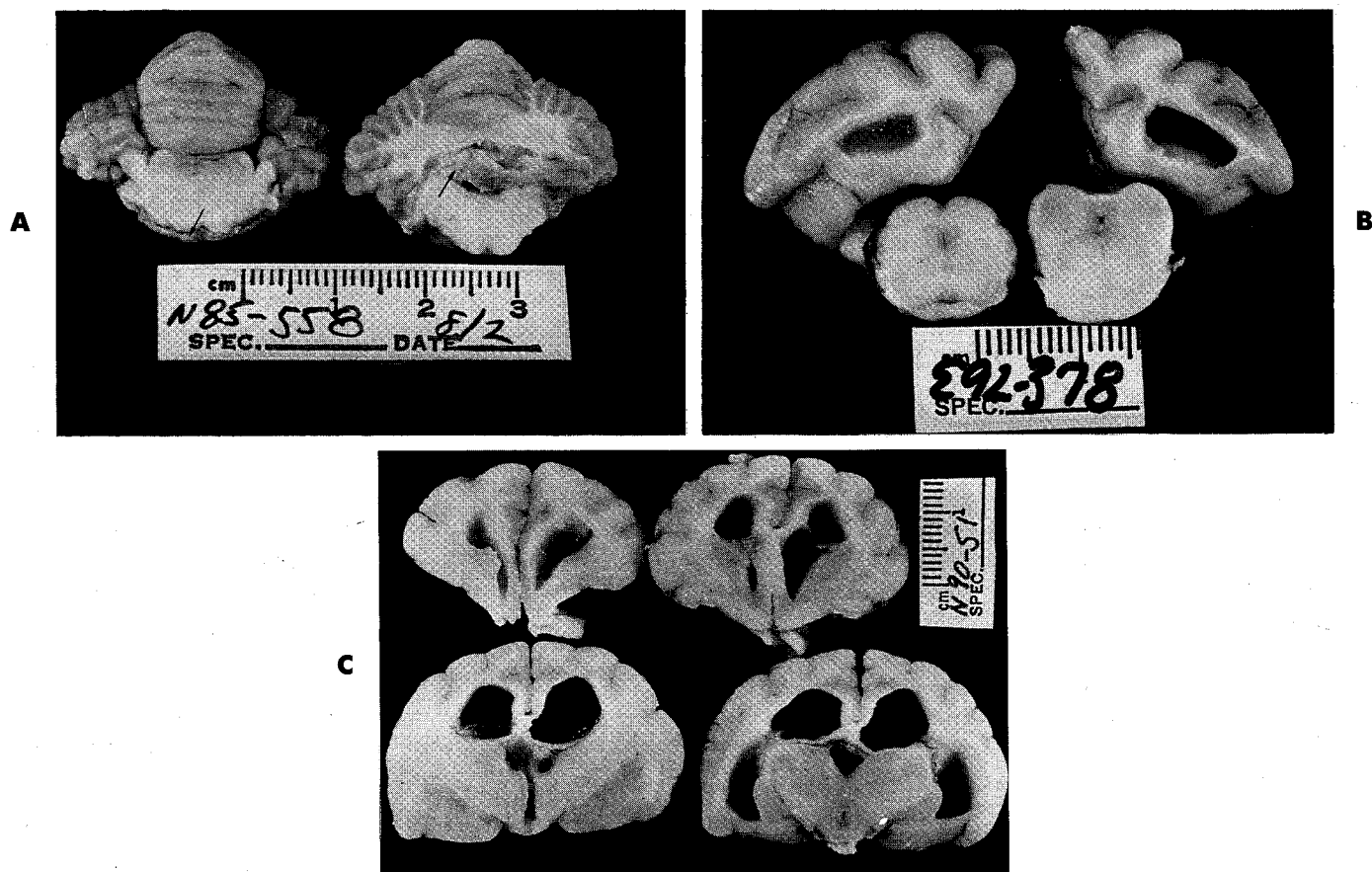


Fig. 3-20. Feline infectious peritonitis. **A**, Thickened leptomeninges and choroid plexus (*arrows*), cerebellum and medulla. **B**, Exudate precipitated in aqueduct and dilated lateral ventricles. Exudate in lateral ventricle. **C**, Hydrocephalus of lateral and third ventricles.

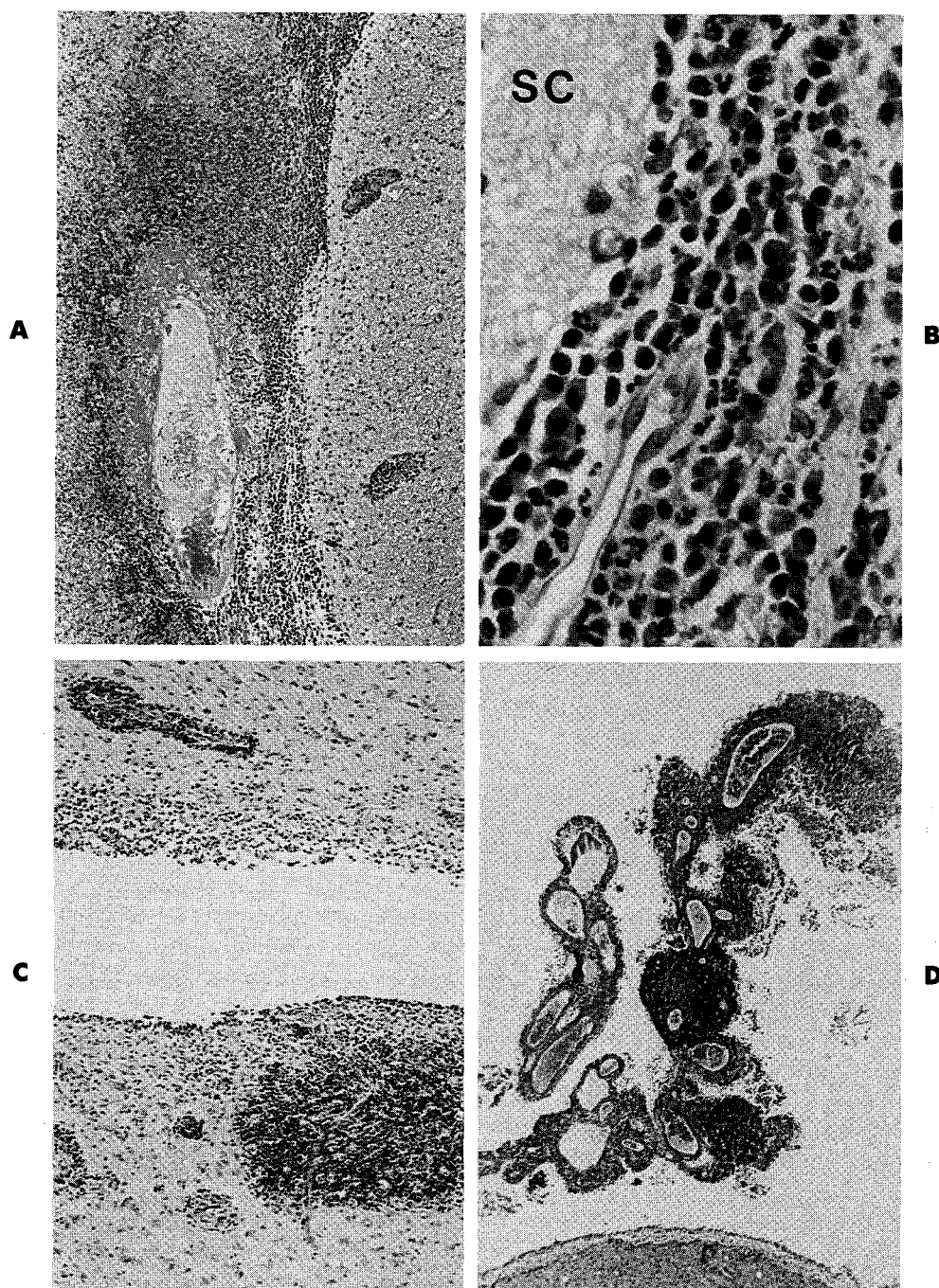


Fig. 3-21. Feline infectious peritonitis. **A**, Leptomeningitis and vascular degeneration, spinal cord. (H&E, $\times 90$.) **B**, Plasma cell and neutrophil infiltrate in subarachnoid space; spinal cord (sc). (H&E, $\times 715$.) **C**, Chronic ventriculitis, thalamus. (H&E, $\times 90$.) **D**, Inflammation of choroid plexus, lateral ventricle. (H&E, $\times 45$.)

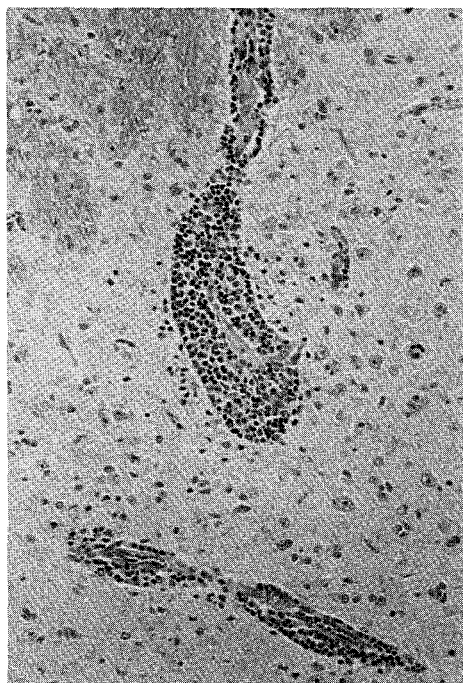


Fig. 3-22. Feline nonsuppurative encephalitis. Perivascular cuffs, brain stem. (H&E, $\times 180$.)

columns of the spinal cord may be severe and are accompanied by a Wallerian degeneration in lateral and ventral funiculi.² Viral inclusions have not been described, and attempts at viral isolation have been unsuccessful.³ Hoff and Vandeveld⁴ described their experience with 16 cases: 6 were typical, while 10 had milder lesions that were more common in the cerebral cortex and basal nuclei, perhaps suggesting that there are two distinct syndromes. In terms of etiological agents, besides a putative feline enterovirus alluded to previously, the feline immunodeficiency virus⁵ may also be a candidate, although serological studies for feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV) have been negative.⁶ In one study of 24 cats with this disorder, 44% had antibodies to Borna virus.⁷

Similar examples of a nonsuppurative encephalomyelitis have been observed in lions and tigers kept in zoological gardens.⁸

References are on page 176.

FELINE IMMUNODEFICIENCY VIRUS ENCEPHALOMYELITIS

In 1987, Pedersen and his colleagues at the University of California described the isolation of a T cell lymphotropic virus from cats with an immunodeficiency-like syndrome.¹ Further reports from the United States and other countries soon established that infection with FIV is quite prevalent in domestic cats worldwide.² The FIV is a lentivirus³ resembling human and simian immunodeficiency viruses⁴ and

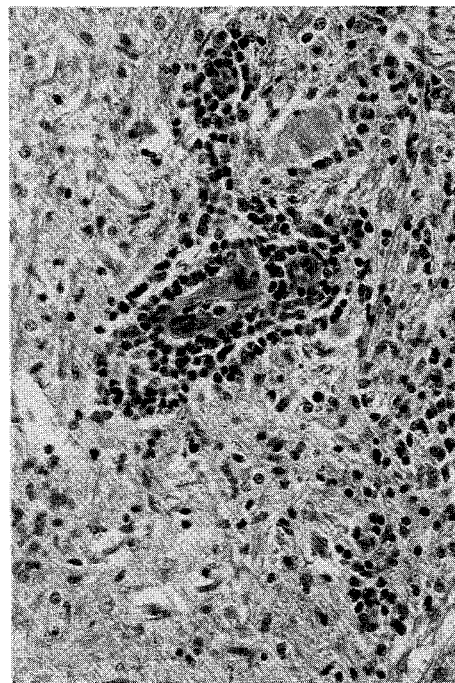


Fig. 3-23. Feline immunodeficiency virus encephalitis. Lymphocytic cuffing and gliosis, cerebellum. (H&E, $\times 350$.)

is mostly isolated from cats with chronic oral, upper respiratory tract, enteric, and conjunctival infections.⁵

A neurotropic potential of FIV is to be anticipated, given the clinical expression of infection with the human immunodeficiency virus and the various animal lentiviruses. Behavioral abnormalities, twitching, and ataxia have been observed in a small proportion of FIV-infected cats,^{5,6} but the frequency of CNS infection may be much more common than this would suggest. In experimentally infected cats, a mild, nonsuppurative meningoencephalitis (Fig. 3-23) with glial nodules and mononuclear cell perivascular cuffing has been observed in gray and white matter.^{7,8} The CSF showed a pleocytosis and evidence of local IgG production.⁹ In naturally infected cats, antibodies could be detected in and FIV cultured from the CSF.¹⁰ The importance of this feline agent as a cause of CNS disease remains to be established.

References are on page 176.

FELINE DEMYELINATING OPTIC NEURITIS

Morphological studies of the central nervous systems of 235 clinically normal mature cats were performed by Cook and Wilcox.¹ Surprisingly, 16 of these animals contained multifocal, inflammatory, demyelinating lesions; plaques were most prominent in, but not confined to, the optic nerves. Light and electron microscopic examination revealed primary demyelination accompanied by infiltrates of lymphocytes, plasma cells, and macrophages. Older lesions showed astroglial scar formation. Cocultivation of CNS cells from three cats have yielded structures said to resemble

paramyxoviral nucleocapsids.² However, the identity of these structures and their demonstration as the causative agent are yet to be established.

It is curious that this syndrome has not been more widely encountered by other pathologists or other investigators, considering the wide use of the cat in neurophysiological and related studies.

References are on page 176.

ENTEROVIRUS ENCEPHALOMYELITIS

Enteroviruses of humans and animals are so named because they inhabit the alimentary (enteric) tract. Their dissemination to other tissues may be associated with clinical disease; enteroviruses are the cause of aseptic meningitis, respiratory infections, and hepatitis in humans. Of particular importance was human poliomyelitis which occurred in epidemic form, but for which effective vaccines are now available.

In the animal species with which we are concerned, CNS enterovirus infection is of significance in the **pig**. Neurological disease has been identified and studied in several countries, and several eponyms have gained common usage in defining these porcine encephalomyelitides. These designations were particularly valuable before the nature of the etiological agent was established and were employed because there was similarity—but not absolute identity—among the various syndromes recognized. To complicate matters further, the characteristic neuropathological changes in enterovirus infection of the CNS (nonsuppurative polioencephalomyelitis) occur in several other viral infections of swine. These include hog cholera, swine vesicular disease, hemagglutinating encephalomyelitis virus, encephalomyocarditis virus, Aujeszky's disease, and rabies. Little wonder that microbiological and serological studies have been crucial in clarifying the picture in viral infections of the CNS in swine.

To return to the porcine enteroviruses, it appears that there are several antigenically related strains of the agent. Following studies of the syndrome in Czechoslovakia, the name Teschen disease was applied by Trefny in 1930. Then followed poliomyelitis suum from Denmark¹ and benign enzootic paresis and Talfan disease in the United Kingdom.² Ontario encephalomyelitis of piglets in Canada^{3,4} was probably hemagglutinating encephalomyelitis virus infection (vomiting and wasting disease) and not enterovirus infection, as was believed at the time.

Clinical disease is seen in postweaning pigs. Teschen and Talfan forms occur at approximately 6 to 10 weeks of age, with variable morbidity and mortality. Of the two, Teschen disease is more virulent. In Denmark, disease is commonly encountered up to 16 weeks and sometimes beyond; these strain-related aspects are reviewed by Mills and Nielsen.⁵ Neurological infection may be fulminating with fever and mild ataxia, rapidly progressing to seizures, opisthotonus, coma, and death. Subacute forms begin as vague limb pa-

resis, progressing in a few days through apparent ataxia to flaccid paraparesis or paraplegia. Sometimes all limbs are paralyzed and unable to support weight. Affected pigs recline on their sternums, remain quite bright, and will eat if they can get to their feed. In commercial operations such affected pigs would be disposed of, but, if retained, some degree of recovery is possible.

The pathological findings are microscopic and involve the entire neuraxis and craniospinal ganglia. There are areas of predilection within the CNS, and, not surprisingly, these vary with the viral strain in question. Accordingly, the following description is generic rather than precise for any particular agent. There is a nonsuppurative encephalomyelitis, involving gray matter areas much more than white matter. In the spinal cord (a consistent target area) there is progressive lymphocytic perivascular cuffing and infiltration of mononuclear cells into the neuropil. Infiltrates occur in response to motor neuron degeneration in the ventral gray columns; changes in the dorsal horn are milder. Initially, affected neurons swell slightly, their Nissl bodies become granular, and the nucleus hyperchromatic and eccentrically located. Some progress to near-total chromatolysis or vacuolation of the soma, which begins at the periphery.⁶ Other neurons are contracted and densely eosinophilic. Degen-erating neurons attract local microglia. Perineuronal microglial satellitosis progresses to neuronophagia,⁷ and neuronal demise is marked by glial nodule formation. These glial stars are one of the hallmarks of the neurotropic viral infections and are conspicuous in this disease. There is a moderate diffuse gliosis also. Lesions in spinal cord white matter, in contrast, are mild and much less frequent.

Similar gray matter lesions are found in the pontine nuclei, medulla, cerebellar cortex, thalamus, periaqueductal gray matter, and cerebral cortex. Leptomeningitis is patchy except for the cerebellum, where it may be pronounced. The cellular pathology is similar to human poliomyelitis, but there are differences in terms of severity and distribution of lesions.⁶ In pigs that survive, neuronal depletion, a mild persisting lymphoplasmacytic infiltrate, and astrocytic scarring are found. Cerebellar involvement may result in cortical atrophy. Wallerian degeneration in the peripheral nerves occurs as a sequel to destruction of lower motor neurons⁸ in the spinal cord.

Further characteristic changes will be found in the spinal and cranial ganglia, particularly the former. There is a lymphocytic influx, sometimes heavy, and degeneration of scattered ganglion cells. Neuronophagia is much less frequent than in the CNS. If neuronal degeneration in the spinal ganglia is severe, Wallerian degeneration will be found in the dorsal roots and the ascending pathways in the dorsal funiculus of the spinal cord.²

Ultrastructurally, changes in motor neurons proceed from separation of ribosomes from the endoplasmic reticulum and loss of Nissl body clusters to a progressive dilation of the endoplasmic reticulum,⁹ producing a vesicular network.

Current concepts of the pathogenesis of enterovirus infections envision three phases: (1) local replication in the gut, mucosal lymphoid tissues (tonsils, Peyer's patches), and the local lymph nodes; (2) viremia; and (3) CNS invasion. Infection appears to be selective for specific neuronal populations,¹⁰ resulting in the characteristic clinical syndrome of lower motor neuron paralysis. The predilection for spinal cord ventral horn cells has been shown with human poliovirus in mice.¹¹

In **chickens**, a polioencephalomyelitis caused by an enterovirus is seen in young birds. This syndrome is known as avian encephalomyelitis or epidemic tremor. Morbidity and mortality are most severe in the first few weeks of life¹² and reflect a susceptibility resulting from immaturity of the immune system, particularly the humoral component.^{13,14} Affected chicks have a limb paresis or paralysis and sometimes a tremor of the head. The neuropathological changes mimic the mammalian enteroviral infections, producing chromatolyzed (Fig. 3-24) and shrunken, degenerate motor neurons in the brain stem and spinal cord, as well as non-suppurative inflammation.^{15,16} Ultrastructurally, affected neurons show a progressive vacuolation of the granular endoplasmic reticulum, loss of attached and free ribosomes, destruction of Golgi cisternae, and mitochondrial vacuolation and loss of cristae.^{14,17}

Theiler's disease of **mice** is caused by an enterovirus that commonly persists subclinically in mice colonies. Isolated

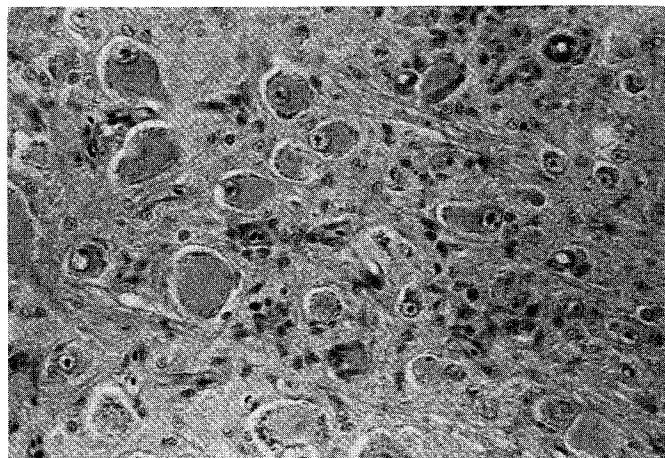


Fig. 3-24. Enterovirus encephalomyelitis, chicken. Chromatolyzed spinal cord neurons. (H&E, $\times 350$.)

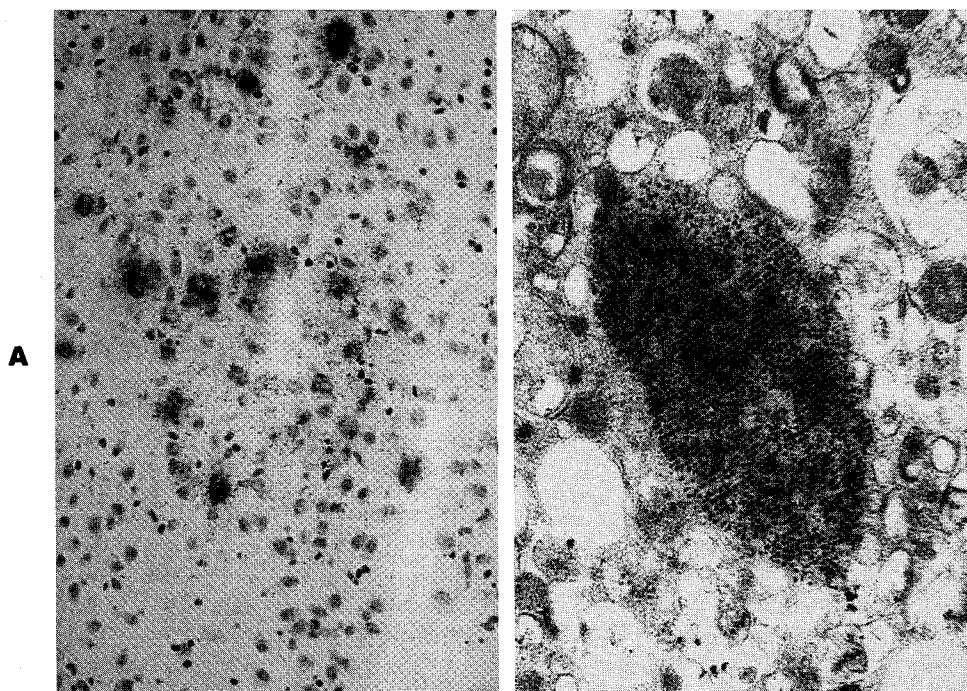


Fig. 3-25. Theiler's disease, mouse. **A**, In situ hybridization showing neuronal infection in gray matter. **B**, Paracrystalline array of virus within a degenerate oligodendrocyte. ($\times 35,300$.)

by Theiler in 1937¹⁸ from a young mouse with flaccid paralysis of the pelvic limbs, this agent is an uncommon cause of spontaneous CNS disease in mice populations but has become a popular tool for the study of virus-induced demyelinating disease. Following intracerebral inoculation, a biphasic pattern of disease ensues¹⁹ that is influenced by both the age at inoculation and the virus strain.^{20,21} The early phase is marked by flaccid paralysis, a consequence of a polioencephalomyelitis that involves gray matter of the brain stem and spinal cord (Fig. 3-25, A). In neonates, the mortality is high with extensive neuronal necrosis and microgliosis. However, if weanlings are inoculated, a proportion survive, only to develop a delayed spastic paralysis by 8 to 12 weeks. This second stage is associated with viral persistence in the CNS (up to a year has been recorded) with mononuclear cell infiltrates in the spinal cord leptomeninges and white matter. Populations of lymphocytes, macrophages, and plasma cells are associated with patchy areas of demyelination, seen ultrastructurally as vesicular degeneration of myelin and stripping by macrophages.²² The effects of immunosuppression of the host, after infection, suggest that the early gray matter phase is a result of virus-induced cytolysis, whereas the effects on white matter are immune-mediated.²³ In white matter, virus is believed to first infect astrocytes and macrophages and then to persist in oligodendrocytes (Fig. 3-25, B).²⁴ Demyelination resulting from immune-mediated injury to virus-infected oligodendrocytes has been proposed.²⁵ Another contributing factor may be antibody, generated in response to Theiler's virus infection, that cross-reacts with oligodendrocytes and myelin and can amplify demyelination.²⁶ Infection does result in some demyelination in nude mice, suggesting a direct viral effect on the oligodendrocyte also.²⁷ The direct effect of virus may be more important than is currently thought, perhaps with infection being introduced, or activated, in normal white matter by infiltrating mononuclear cells.²⁸

Attempts to localize the basis for neurovirulence within the genome of Theiler's virus have been reported.²⁹⁻³¹ One study²⁹ suggested that neurovirulence maps to the nucleotide sequence encoding the surface (coat) proteins, which may influence susceptibility of neurons to infection via specific receptors. It is probable that the determinants of pathogenicity are polygenic.

The occurrence of enteroviruses in other animal species is well documented, but their role in neurological disease is not established. Occasional episodes of idiopathic polioencephalomyelitis are seen in **cats**^{32,33} and **cattle**,³⁴ and a role for enteroviruses in these syndromes may be worth pursuing.

References are on page 176.

MISCELLANEOUS CAUSES OF PORCINE ENCEPHALOMYELITIS

Hog cholera
African swine fever
Vomiting and wasting disease
Swine vesicular disease
Encephalomyocarditis virus
Paramyxovirus

Encephalomyelitis in the pig, more than for any other species, is associated with a considerable number of viral agents (see Table 3-1). In this volume, several have been discussed—the enteroviruses (Teschin-Talfan group), Aujeszky's disease, and rabies—all of which are neurotropic. Central nervous system infection is also associated with a number of systemic viral diseases of swine; clinical and pathological aspects are reviewed by Saunders,¹ Done,² and O'Hara and Shortridge.³

Hog cholera

Hog cholera (HC) or **swine fever** (as it is known in the British commonwealth countries) is one of the true animal plagues. This porcine disease is a systemic viral infection caused by a pestivirus (family *Togaviridae*) closely related to bovine virus diarrhea agent. Strains of varying antigenicity and widely differing virulence exist in the field, resulting in a disease picture that covers the spectrum from fulminating infection with high morbidity and mortality to virtually inapparent disease.⁴ Many countries have adopted

Table 3-1. Causes of nonsuppurative encephalomyelitis and/or ganglionitis in swine

| |
|---|
| Enteroviruses |
| Hog cholera and swine fever (primary vasculitis) |
| Vomiting and wasting disease—hemagglutinating encephalomyelitis virus |
| Rabies |
| Aujeszky's disease |
| Swine vesicular disease |
| Swine paramyxovirus |
| Encephalomyocarditis virus (mild CNS lesions) |
| Japanese encephalitis virus |
| Louping ill |
| Porcine reproductive and respiratory syndrome (mild CNS lesions) |

eradication programs, and HC is not recognized in Canada, the United States, England, Australia, and Scandinavia. In many European and Central American nations, it is rife.

Clinical disease may run a peracute, acute, subacute, or chronic course. Acute illness caused by highly virulent strains is perhaps the most classical; there is high fever, anorexia, severe depression, leukopenia, and constipation that gives way to watery diarrhea. Neurological deficits may appear, including a staggering gait and seizures. Death ensues in 1 to 3 weeks. Viral strains of lower virulence induce milder patterns of disease that spread more slowly and take a subacute to chronic course.

Necropsy findings in acute cases are marked by disseminated visceral hemorrhages, a consequence of endothelial degeneration, thrombocytopenia, and coagulation disorders. Neuropathological changes have some specificity^{5,6} as they reflect primary injury to small blood vessels. Capillary and venular vasculitis (Fig. 3-26) is widely disseminated in the CNS with equal involvement of gray and white matter. Topographically, lesions are most common in the brain stem.⁵ There is infiltration into the vascular wall and its pericytic/adventitial sheath with lymphocytes and histiocytes. Such cuffs vary from one to several cells in breadth. Endothelial swelling may be prominent, encroaching upon the vascular lumen. Capillary hemorrhages are sprinkled around, but thrombosis is lacking. Parenchymal inflammation is related to these involved blood vessels. Secondary changes in the parenchyma (microinfarcts) with focal microgliosis and a lymphocytic meningitis are less frequent.

Infection of pregnant sows by HC virus often results in fetal loss with abortion or mummification. Some strains are teratogenic, producing fetal hypomyelination and cerebellar hypoplasia. Thus HC is one cause of the congenital tremor syndrome of pigs, and this form is classified as congenital tremors type A1.⁷

African swine fever

Like classical swine fever, **African swine fever (ASF)** is a disease of remarkable variation in its clinical severity, ranging from peracute to inapparent. It is caused by a DNA virus of the genus *Iridovirus* (family Iridoviridae) and in Africa is maintained in unaffected warthogs and possibly other hogs. Soft ornithodoros ticks are also virus reservoirs and are important in transmission. It has spread from Africa to Spain, Portugal, Cuba, Brazil, and the Dominican Republic. Feeding pigs with uncooked garbage (containing pork scraps) from ships and aircraft has often been incriminated or suspected as the source.

Clinically and pathologically the syndrome resembles hog cholera.⁸ There is extremely high fever, apathy, depression, tachypnea, diarrhea, and death. At necropsy, disseminated petechial to extensive hemorrhages are prominent, especially in lymphoid organs. Fluid accumulates in the thorax and pericardium. The CNS changes are microscopic and are seen mainly in association with virulent strains of the agent. There is profound vascular endothelial degeneration and

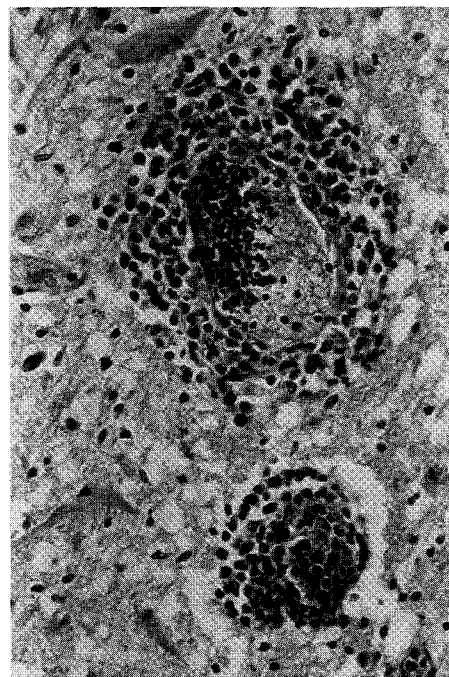


Fig. 3-26. Hog cholera. Lymphocytic vasculitis, medulla. (H&E, $\times 350$.)

lymphocytic cuffing. Diagnosis is made by virus demonstration in a hemadsorption test, immunofluorescent procedures, and transmission studies.

Vomiting and wasting disease

The earliest report of **vomiting and wasting disease (VWD)** was probably by Roe and Alexander,⁹ who described a highly fatal disease of suckling piglets in Ontario. Acutely affected animals were mostly under 3 weeks of age, and the morbidity in a litter was high. Disease was manifest as inappetence, vomiting, excessive salivation, huddling together, and, after a few days, severe constipation. Some became moribund and died, but many followed a chronic course of progressive emaciation and stunting that could last for weeks. This syndrome, often occurring in epidemic form in young piglets, was thus designated VWD¹⁰ and was subsequently recorded in England¹¹ and continental Europe.

Soon after Roe and Alexander's report, descriptions of a transmissible encephalomyelitis of young piglets were published, also from Ontario.¹²⁻¹⁴ This syndrome also affected piglets of a few days of age and ran a course of constipation, lethargy, and sometimes vomiting, progressing in a few days to hyperesthesia, muscle tremors, a jerky stilted gait, paresis, ataxia, prostration, coma, and death. In 1962, Grieg et al¹⁵ recorded the isolation of a hemagglutinating viral agent from several cases of encephalomyelitis in 7- to 8-day-old piglets in eastern Ontario. This agent, often described as the **hemagglutinating encephalomyelitis virus (HEV)** has subsequently been characterized as a porcine coronavirus and shown to be capable of pro-

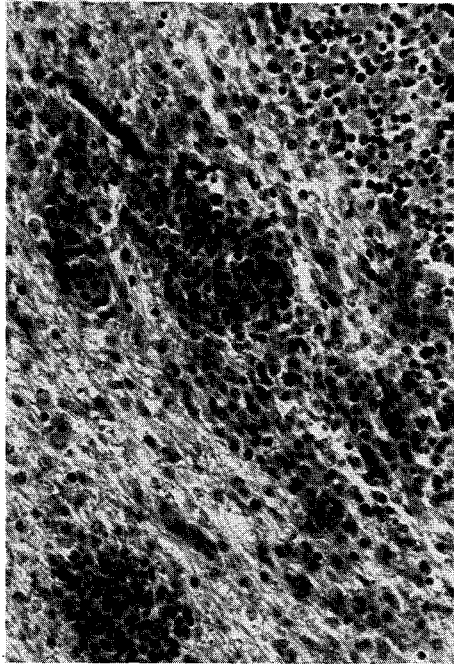


Fig. 3-27. Vomiting and wasting disease. Glial nodules in the medulla of the cerebellum (granule cells, upper right). (H&E, $\times 350$.)

ducing both the vomiting and wasting syndrome, and the encephalitic disease.¹⁶ The neurological syndrome was designated Ontario encephalomyelitis and at first was thought to be related to Teschen-Talfan disease of pigs (enterovirus infection).

In the field, there is some overlap of these two syndromes (gastrointestinal versus neurological) in individual piglets, perhaps most evident in the Canadian experience.¹² Thus piglets may initially be anorectic, lethargic, and occasionally vomit, progressing in a couple of days to overt neurological disease. Both forms of the disease are most common in piglets under 3 weeks of age; the pure encephalitic disease is usually seen earlier, and its course is shorter. In contrast, piglets runted with VWD may survive for weeks. This merging of the two syndromes is further exemplified by the reports from Cartwright¹⁷ of a viral isolate from a piglet showing VWD probably identical to the Canadian HEV virus. Cartwright further commented that the English pathologist David Harding observed CNS lesions in approximately 25% of cases of VWD. In experimental transmission studies, Appel et al¹⁸ similarly observed lesions of viral encephalitis (in one litter) in the absence of neurological disease in all but one piglet.

The gross pathological changes in piglets that die with VWD are often unremarkable. In acute deaths there may be gastric dilation with accumulation of ingesta but little more to see; chronic survivors are severely runted and emaciated. There are degenerative and inflammatory changes in the ganglia in the stomach wall involving 15% to 85% of cases.¹⁹ A proportion show a nonsuppurative encephalo-

myelitis (Fig. 3-27) and also a pneumonitis. Piglets that die following overt CNS disease manifest a disseminated non-suppurative encephalomyelitis and ganglionitis of cranio-spinal and autonomic ganglia.^{13,20} There are no gross changes in the nervous system. Microscopically there is widespread inflammation, predominantly involving the gray matter of the brain stem. Neuronal degeneration is marked by shrinkage and condensation of the soma, satellitosis, and neuronophagia. Nodules of microglial cells are admixed with lymphocytes, which migrate in from nearby perivascular cuffs. Cuffing and gliosis are more conspicuous than neuronal changes. Meningeal involvement is variable in severity. Viral antigen can be demonstrated in the trigeminal ganglion 3 days after oral infection.²¹ Electron microscopic studies have demonstrated that the target for this coronavirus infection is neurons, and virions are usually found within cisternae of endoplasmic reticulum or the Golgi complex.²²

Serological studies indicate that this infection is common, approaching 100% in adult swine.^{23,24} If sows are immune, colostrum antibody protects the suckling piglets. Neonatal piglets from nonimmune dams are susceptible to infection and disease, and in such situations epidemics involving virtually 100% of the animals in multiple litters can occur. Infection of older pigs appears to be innocuous, although sows may show a transient illness during a disease outbreak. The basis for the two disease patterns is unclear but may relate to differences in viral and perhaps animal strains. Five viral isolates from five U.S. epidemics produced acute neurological disease in some recipients and a subacute VWD in others.¹⁶

Pathogenesis studies reveal initial viral replication in the nasal mucosa, tonsils, lungs, and small intestine, followed by replication in enteric and gastric ganglia, other peripheral autonomic ganglia, cranial ganglia (especially trigeminal and distal vagal), and the brain stem, particularly the nuclei of the spinal tract of the trigeminal nerve and the solitary tract in the medulla.²⁵ A case is thus made for dissemination along peripheral and cranial nerves to ganglia and the CNS. Whether the vomiting and subsequent constipation pattern of disease is a consequence of injury to the enteric nervous system or the brain stem is yet to be established. Potentially, however, HEV-induced VWD could be described as an infectious dysautonomia.

Swine vesicular disease

Swine vesicular disease (SVD) first appeared in Italy in 1966 and subsequently was recorded in several European countries and parts of Asia.²⁶ The causative agent is an enterovirus closely related to human coxsackie B5 virus, and, indeed, human infection with the porcine virus can occur. The importance of this relatively new porcine disease relates to its epitheliotropism, resulting in vesicular lesions of the hoofs, snout, and tongue that clinically are indistinguishable from foot and mouth disease (and other vesicular diseases of swine).

Neurological signs have infrequently been recorded in

adult pigs during disease outbreaks,²⁷ but by histopathological examination a nonsuppurative encephalomyelitis is consistently observed. Such lesions have been studied in experimentally infected pigs.²⁷⁻²⁹ Lesions are quite disseminated in the brain, particularly the brain stem, and less pronounced in the spinal cord. There is perivascular cuffing with lymphocytes and monocytes, as well as focal to diffuse gliosis in gray and white matter. Neuronophagia is not prominent, but foci of malacia are found. Ganglionitis involves craniospinal and autonomic ganglia. Neuronal satellite cells may contain amphoteric, intranuclear inclusions. Ultrastructurally, these bodies contain granular and fibrillar elements but lack virions and may be nonspecific.²⁷

Clinically SVD presents in multiple animals as modest pyrexia, acute lameness, and vesicle formation and so is quite different from the other encephalitides. The agent is transmissible to neonatal mice, resulting in paralysis and death in 5 to 10 days.²⁶

Encephalomyocarditis virus

Encephalomyocarditis (EMC) virus is a picornavirus carried by rodents, particularly mice and rats. Infection and mortalities in swine herds have been recorded in the United States,³⁰ Australia,³¹ and elsewhere. Disease is usually seen in pigs between 3 and 20 weeks of age with a mortality of up to 50% of the population. At the extremes of susceptibility (3 weeks and 4 to 5 months) mortalities may approach 100%. Sudden death is the usual presentation, although a short course of depression, staggering, and collapse may be noted. Acute deaths result from viral myocarditis, and at necropsy discrete pallid areas of myocardial necrosis are evident in the ventricular muscle. There is hepatic and pulmonary congestion, consistent with acute heart failure. A minority of affected pigs also have a trivial nonsuppurative meningoencephalitis.³¹ Epidemics often coincide with plagues of mice or rats, and pigs are probably infected from eating dead rodents. The disease is transmissible to pigs by several routes,³² but pig-to-pig spread is probably unimportant. Subclinical infection is common, and myocardial lesions may be found incidentally in pigs sent to slaughter. Viral strains of differing virulence appear to exist; in England there is serological evidence of infection in the absence of overt disease.³³ Recent studies incriminate encephalomyocarditis virus as a cause of reproductive losses in swine with encephalitis and myocarditis in mummified and still-born piglets.³⁴

Paramyxovirus

A novel syndrome of encephalomyelitis of swine associated with a **paramyxovirus** has been reported from Mexico.³⁵ Disease is seen in young piglets up to 3 weeks of age, and is explosive but self-limiting. Some piglets are found in a state of collapse while others show ataxia, paresis, and muscle tremor. Up to 10% have unilateral or bilateral corneal opacity, frequently without other signs. Most sows are clinically normal, and pigs over 30 days of age have only mild,

transitory disease. Pregnant sows may abort, and stillbirths are seen. The pathology is microscopic; there is diffuse polioencephalomyelitis with neuronal necrosis and neuronophagia. Inclusion bodies are not found. Pneumonitis and anterior uveitis are also present. The syndrome is transmissible to day-old piglets, and classification of the agent in the genus *Paramyxovirus* has been proposed.³⁶

References are on page 177.

CAPRINE ARTHRITIS ENCEPHALITIS SYNDROME

In 1974, Linda Cork et al described a viral leukoencephalomyelitis of goats.¹ We now recognize this neurological disorder as one manifestation of a multisystemic lentivirus infection in the goat. In addition to demyelinating encephalomyelitis, pneumonitis, polyarthritis, and mastitis are part of the syndrome. A group of related lentiviruses of sheep cause remarkably similar diseases (visna, maedi, and ovine progressive pneumonia) in that species. As well as in the United States, this caprine encephalomyelitis has been described in Australia² and Switzerland³ and most likely occurs elsewhere.⁴

The agent is transmitted to kid goats early in life in the colostrum and milk and probably from direct contact with infected dams.⁵ In utero transmission appears to be uncommon. Neurological disease is seen in young kids, mostly 2 to 4 months of age,^{6,7} and sporadically in older animals. Arthritis (and bursitis), pneumonitis, and mastitis are clinical problems in adult goats.

In young goats CNS disease is usually acute in onset and rapidly progressive. Clinical signs depend on the location of the lesion(s); most cases present as spinal cord or caudal brain stem disease. Generally, neurological signs reflect upper motor neuron and general proprioceptive deficits, as the lesions predominate in white matter. Focal thoracolumbar myelitis may present as a spastic monoparesis or paraparesis and progress to paraplegia in a few days. If the spinal cord lesion is more diffuse, tetraparesis or tetraplegia may develop. Unilateral cervical spinal cord lesions produce a spastic hemiparesis or hemiplegia, a common presenting scenario. Lesions may extend from the white matter into the adjacent gray matter to produce lower motor neuron disease, but this is less common.⁷ Caudal brain stem lesions that cause spastic paresis and ataxia with balance loss, head tilt, and torticollis are quite frequent. Least common are predominantly behavioral changes, visual deficits, and abnormal postural reactions, indicative of cerebral disease. Although initially the neurological disease progresses rapidly, it may become static; slight improvement has been reported, but significant recovery is unlikely.

Cerebrospinal fluid reflects the extensive degeneration and inflammation within the neuraxis. Both elevated protein and pleocytosis are to be anticipated; cells are mainly lymphocytes and monocytes. At necropsy, gross lesions are often seen upon sectioning the brain and spinal cord. One

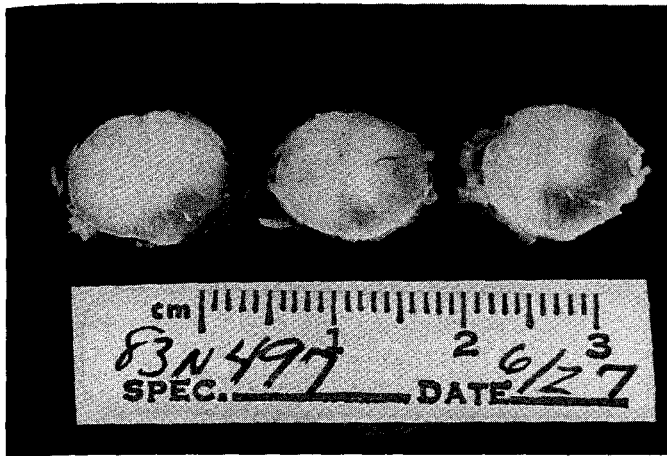


Fig. 3-28. Caprine arthritis encephalitis syndrome. Areas of dense inflammation and degeneration in the spinal cord white matter are seen as areas of discoloration.

remarkable adult case at Cornell had massive white matter necrosis and mineralization in the cerebrum, evident from the surface of the brain. Affected white matter is dull white to brown with a firm consistency, and lesions may be disseminated from the frontal lobes to the conus medullaris. Cerebral lesions are often periventricular; spinal cord lesions (Fig. 3-28) may be asymmetric, sometimes producing severe swelling of the tissue on the affected side. Microscopically, findings are of severe nonsuppurative inflammation (Fig. 3-29, A and B) with dense perivascular cuffing by lymphocytes, monocytes, and plasma cells. Mononuclear cells percolate into the white matter, which is pale and rarefied and harbors many reactive astrocytes including sporadic multinucleated forms. White matter lesions progress from demyelinating to necrotizing, the latter sometimes associated with mineralization of the tissue. In chronic cases there is a perivascular adventitial fibrosis. Inflammation may extend into the gray matter, for example, in the spinal cord or cerebellar nuclei. Neurons survive surprisingly in a sea of mononuclear leukocytes, but the occasional chromatolytic cell body will be encountered. Ultrastructural studies have demonstrated the demyelinating nature of the lesion (Fig. 3-29, D), with macrophages stripping myelin from axons.⁸ In the interstitium are found phagocytes filled with myelin debris and filament-laden processes of fibrous astrocytes.

In areas of the United States where this caprine agent is endemic, infection in goat herds (as measured by the agar gel immunodiffusion test) is 81% of the population.⁹ In contrast, clinical disease occurs in only a small proportion of seropositive goats, which are persistently infected with the virus.¹⁰ Proviral DNA can be detected by the polymerase chain reaction.¹¹ Unlike the closely related visna virus of sheep, caprine arthritis encephalitis virus is a poor inducer of neutralizing antibodies, perhaps a consequence of the quantity or configuration of sialic acid within the viral en-

velope,¹² and viral persistence is associated with low titers of neutralizing antibodies.

It is believed that the encephalomyelitis (and other manifestations of the caprine arthritis encephalitis syndrome) are immune-mediated, akin to visna-maedi;¹³ see reviews by Haase,¹⁴ Dawson,¹⁵ and Peterhans and colleagues.¹⁶ Viral expression, as determined by in situ hybridization, appears to be associated with CNS inflammation,¹⁷ and macrophages are important target cells.¹⁸ As in the ovine syndrome, lentivirus-induced lymphocyte interferon seems to play a central role and has both disease-inhibiting and disease-enhancing effects: It slows macrophage maturation and viral replication while concomitantly enhancing macrophage activation, for example, Ia expression.¹⁹ Why encephalomyelitis develops so rapidly in young goat kids with caprine arthritis encephalitis syndrome whereas visna in sheep emerges slowly over 2 or 3 years is unclear and points to gaps in our knowledge in the pathogenesis of these two closely related lentiviral diseases.

Experimental reproduction of this caprine encephalitis has been difficult and requires intracerebral inoculation; the resulting disease is milder than natural cases. Oral infection of neonatal goats more readily induces chronic joint and mammary gland disease.²⁰ Geographically, varying patterns of disease have been noted (e.g., in Europe, arthritis in goats is more common than CNS disease) and probably reflects differences in viral biotypes and perhaps differences in goat breeds also.

References are on page 177.

VISNA

Visna is the Icelandic term for wasting, which is given to a chronic encephalomyelitis of sheep caused by a lentivirus.^{1,3} Infection with the very closely related maedi agent results in a diffuse interstitial pneumonia accompanied by dyspnea.⁴ Similar if not identical lentiviruses sometimes produce pneumonitis, encephalomyelitis, arthritis, and mastitis of sheep in Europe and North America.^{5,6} Sporadic episodes of visna or a visna-like disease have also been described in goats;^{7,9} one may suspect that these were actually cases of the caprine arthritis encephalitis syndrome (CAES), although the occurrence of CNS disease in adult goats with CAES is much less common than in kids.¹⁰

Visna and maedi have been the focus of considerable study, for they are the prototype of slow viral diseases, characterized by a prolonged incubation period, a slow progressive clinical course, and invariably a fatal outcome.¹¹ Experimental studies in Iceland and the United States suggest that both the virulence of the viral biotype and the breed of sheep influence the course of the infection;¹² for example, Icelandic sheep are more susceptible to visna than are certain British breeds.

The onset of neurological disease after experimental infection may vary from a few months to several years. Natural cases probably involve a latent period of 2 years or more. During this time, serum (and in some cases CSF) contain

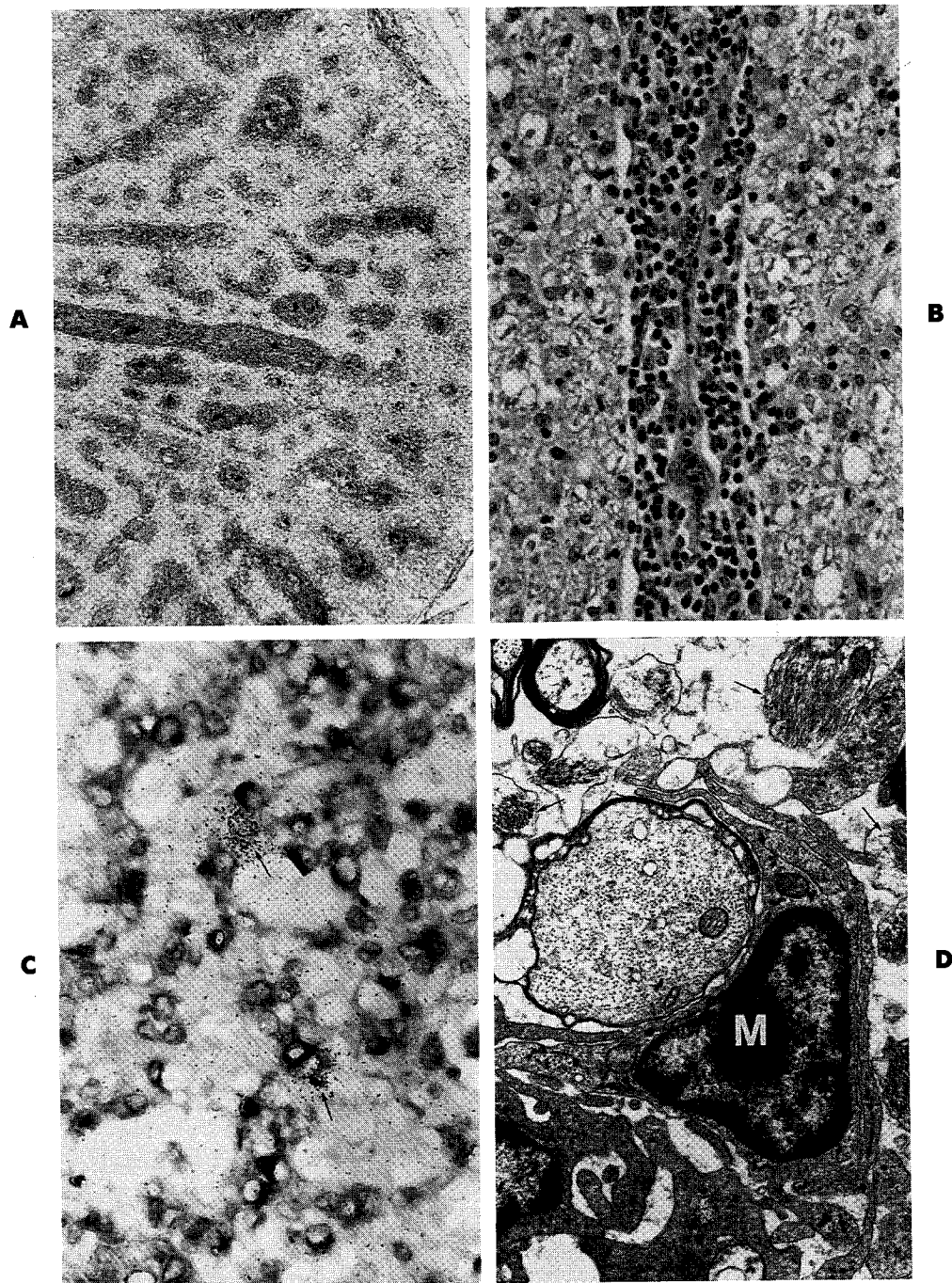


Fig. 3-29. Caprine arthritis encephalitis syndrome. **A**, Perivascular cuffing and myelin loss in spinal cord white matter. (Luxol fast blue, cresyl echt violet, $\times 35$.) **B**, Detail of a perivascular cuff. Vacuolar myelin degeneration and marked astrogliosis. (H&E, $\times 350$.) **C**, In situ hybridization for CAES virus (arrows) in lectin-stained macrophages, spinal cord. ($\times 560$.) **D**, Electron micrograph showing a macrophage (*M*) that extends processes toward an almost totally demyelinated axon. Arrows indicate astroglial processes. ($\times 15,600$.)

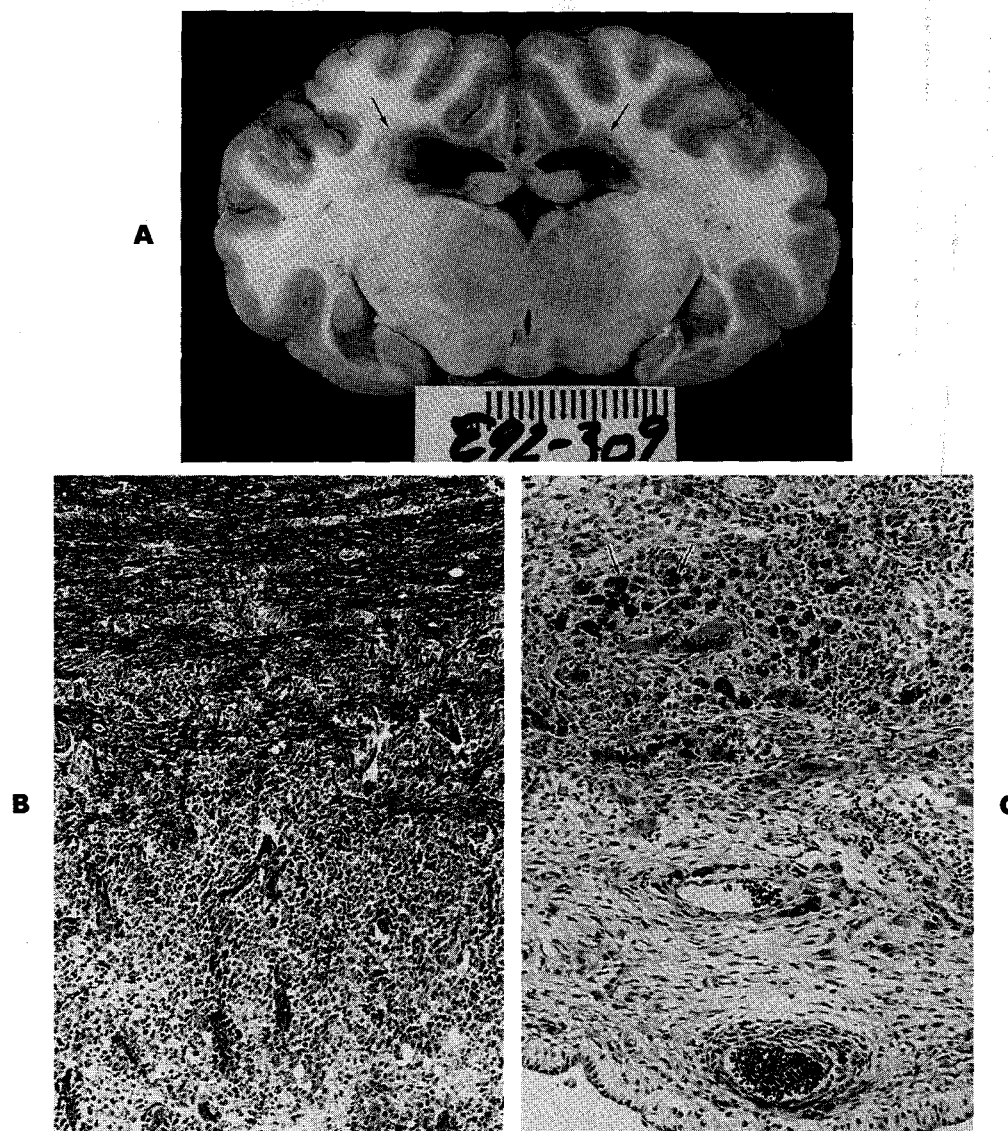


Fig. 3-30. Visna. **A**, Periventricular white matter degeneration (*arrows*). **B**, Inflammation and myelin destruction adjacent to lateral ventricle, cerebrum. (Luxol fast blue, cresyl echt violet, $\times 90$.) **C**, Periventricular inflammation, cerebrum. Darkly stained cells (*arrows*) are myelin-laden macrophages. (LFBCEV, $\times 140$.)

neutralizing antibodies. A mononuclear cell pleocytosis in the CSF, consisting of lymphocytes and macrophages, appears within a week or two of infection, plateaus, but then remains elevated for months.¹³ Cell counts up to 2000 mononuclear cells per deciliter are known, although the pleocytosis may be absent when clinical signs develop.¹⁴ Protein levels in CSF are also elevated. Microscopic lesions in the neuraxis are present soon after inoculation and probably are slowly progressive.

Clinical signs, which begin insidiously, are at first quite subtle and consist of mild pelvic limb paresis. Gait disorder is progressive and sometimes punctuated by slight remissions; it may extend to involve all limbs. There may be abnormal head posture and fine trembling of the lips.¹⁵ Affected sheep remain bright and alert but become wasted and

may be killed because they are tetraplegic and cannot get to feed. The clinical course runs for several weeks or months.

From cases of visna studied postmortem, gross CNS lesions have infrequently been observed. Extensive inflammatory lesions in white matter are evident as areas of yellowish tan discoloration (Fig. 3-30, *A*). Microscopic changes are diffuse throughout the neuraxis, inflammatory, and nonsuppurative; they affect all areas but predominantly white matter. One characteristic feature is a periventricular distribution (Fig. 3-30, *B* and *C*) in a zone adjacent to the ependymal layer and central canal. A detailed neuroanatomical account of the lesions is provided by Sigurdsson and co-workers.¹⁴ Inflammatory foci vary from mild to extensive perivascular cuffings with lymphocytes, macro-

phages, and plasma cells.¹⁶ These cells percolate from the cuffs into the neuroparenchyma, forming diffuse infiltrates and focal granulomas. White matter involvement predominates, but neuronal areas are affected, for example, the spinal cord gray columns and commissural gray matter around the central canal. In areas of cellular inflammation, myelinated tracts become progressively vacuolated and pallid. A reactive astrocytosis is present but overshadowed by the weight of infiltrating hematogenous mononuclear cells. Intense inflammation results in local areas of liquefactive necrosis. Spinal cord involvement is quite characteristic, typically involving the funicular white matter of one half of the spinal cord in a distribution resembling a rather generous piece of pie. Identical spinal cord changes occur in the caprine arthritis encephalitis syndrome. Lesions also occur in the cerebellum, brain stem, and cerebrum, including the basal nuclei. Leptomeningitis is a consistent observation, as is lymphoplasmacytic inflammation of the choroid plexus stroma, which may form lymphoid nodules with germinal centers. The duration of clinical disease and the severity of CNS changes are not necessarily correlated.

Lesions in the white matter may be a Wallerian degeneration¹⁷ with degeneration of axons and myelin or true primary demyelination,¹⁸ the latter occurring in discrete plaques.¹² Comparisons of early and very late lesions have been made.¹⁹ The primary tissue response is inflammatory, whereas rather acellular demyelinated plaques, reminiscent of old multiple sclerosis lesions, are found in very chronic infections. Ultrastructural studies in areas of lymphoplasmacytic inflammation have shown reactive and edematous astrocyte processes, some intact oligodendroglia, and collapsed myelin sheaths around necrotic axons.¹⁷ Visna virus virions were not found, consistent with current understanding that the virus is incorporated into the host cell's genome as proviral DNA. Electron microscopic studies of sheep with very chronic disease have documented foci of primary demyelination with axonal sparing.¹⁸

A periventricular pattern of CNS inflammation is a feature of other immunopathological diseases including feline infectious peritonitis and equine infectious anemia. Immunosuppression of visna virus-infected sheep largely abolished the development of CNS lesions but had little effect on the ability to recover virus,²⁰ thus supporting the immunopathological hypothesis. Expression of visna virus proteins in CNS lesions has been examined,²¹ and there is evidence of oligodendrocyte infection from in situ hybridization studies.²² Such cells could be targets for immune-mediated injury. Narayan, Haase, and their colleagues have provided evidence that the circulating monocyte is the primary viral target,^{23,24} that very few cells are infected, and that viral expression is highly restricted. Interestingly, maturation of blood monocytes into tissue macrophages is associated with increased viral permissiveness.²⁴ Down-regulation of viral expression may be important for successful viral persistence, a state that may last for several years. In this way, lymphocyte and macrophage-mediated tissue in-

jury to infected cells in the CNS is kept to a bare minimum. A unique lentivirus-induced interferon appears to be responsible for restricting viral replication in macrophages, although it also enhances Ia expression in these cells.^{25,26} The susceptibility of individual sheep breeds to develop neurological disease and the clinical course seem to be correlated with the permissiveness of tissue macrophages for viral replication.²⁷ In marked contrast to the situation in vivo, there is no restriction of viral activity in tissue culture with the majority of cells infected and highly productive.

During the chronic course of the infection, antigenic drift of the virus may occur,²⁸ but this is thought to be uncommon²⁹ and of minor biological importance in the scheme of viral persistence within the host.¹² Proviral DNA can be detected in infected cells by the polymerase chain reaction.³⁰

References are on page 178.

LOUPING ILL

Louping ill is a tick-borne flavivirus infection that occurs in Scotland, northern England, Ireland, Norway, and perhaps elsewhere in Europe.¹ Infection, as established by seropositivity, occurs in domestic animals, humans, small mammals, rodents, and birds. Clinical neurological disease is most common in sheep, occurs less frequently in cattle, and rarely occurs in other species.

Louping ill is named for the leaping gait of lambs afflicted with this encephalomyelitis. Infection is spread by the sheep tick *Ixodes ricinus* and possibly by other ticks and ectoparasites. The distribution of areas where disease occurs is constrained by the tick and probably also by reservoirs of the virus. Disease in sheep corresponds with seasonal tick activity, peaking in early spring and early fall. In endemic areas, clinical disease occurs mainly in older lambs or naive adult sheep introduced from disease-free areas.

Following inoculation of virus by the vector, viremia and pyrexia are followed, in some sheep, by CNS invasion. Affected sheep show muscle tremors and a jerky, ataxic gait with a characteristic bounding action rather like bunny-hopping. Signs of cerebral involvement with head pressing and blindness may be seen. A second episode of pyrexia accompanies these signs of neurological disease. In a few days these deficits progress to paralysis, lateral recumbency, coma, and death. Specific antibody can be found in CSF,² and presumably there is a mononuclear cell pleocytosis. In cattle, the neurological syndrome is similar, but seizures are more common.³

Pathological findings in sheep that succumb are microscopic. The CNS changes are those of a polioencephalomyelitis and are classical for the neurotropic viruses. A distinct distribution of lesions is found favoring the pons, medulla, spinal cord, and cerebellar cortex (Fig. 3-31).⁴ Neurons are degenerate, often slightly shrunken, and hypereosinophilic or vacuolated with indistinct Nissl bodies and pyknotic nuclei. Such cells are replaced by neuronophagic nodules of microglial cells. Loss of cerebellar Pur-

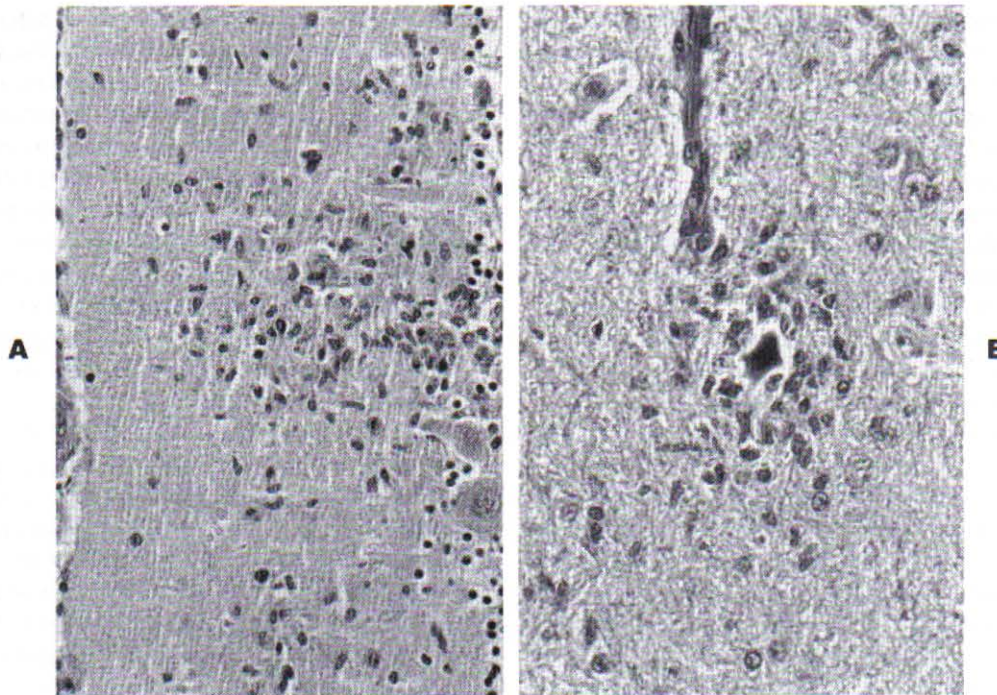


Fig. 3-31. Louping ill, sheep. A, Microgliosis, molecular layer of cerebellum. (H&E, $\times 180$.) B, Neuronophagia, brain stem. (H&E, $\times 560$.)

kinje cells is characteristic, and glial nodules are conspicuous in the normally acellular molecular layer. Perivascular inflammation is largely lymphoplasmacytic, usually with a minor neutrophilic component, and extends to the leptomeninges, especially of the cerebellum. Cuffing in white matter is light. Gliosis is diffuse with focal accentuations at points of neuronal loss. Such lesions are to be found particularly in the reticular formation; hypoglossal, vestibular, trigeminal, and lateral cuneate nuclei; ventral columns of the spinal cord; and cerebellar cortex.^{4,5} Lesions in the midbrain and forebrain are milder. Virus has been demonstrated by electron microscopy within the endoplasmic reticulum of neurons of experimentally infected sheep⁶ and mice.⁷

In endemic areas, the mortality from louping ill is not particularly high, and it appears that many infections are aborted by the immune response before CNS invasion occurs. Following viremia and lymphoid tissue infection in encephalitic cases, viral antigen can be shown to accumulate within neurons of the brain stem and spinal cord.⁶ Neuronal degeneration and necrosis follow viral recruitment of the cellular synthetic apparatus, a common pathway of the lytic neurotropic viruses. Terminally such neurons appear pallid in routine paraffin sections, a consequence of the disrupted Nissl bodies. The severity of clinical signs correlates well with the extent of neuronal damage, which is minimal in surviving animals.⁵

Experimental louping ill infection of calves produced low-titer viremias and neurological signs in one of six.⁸ In cattle, viral invasion of the CNS may be less frequent than

in sheep. Neurological disease caused by this flavivirus has been recorded in horses,⁹ pigs,¹⁰ a dog,¹¹ and a goat,¹² but seems much less common than is subclinical infection in these and other species.¹³ Infection of birds, such as the red grouse, can be lethal.¹⁴

References are on page 178.

LISTERIOSIS

Listeria monocytogenes is a gram-positive bacterium that occurs widely in nature. The organism, which is hardy and long-lived in the environment, may be found in the soil, plants, silage, and feces. Subclinical infections in animal populations are probably common, as attested to by the presence of serum agglutinins in normal animals.¹ On the basis of flagellar and somatic antigens, 7 serotypes and 14 subtypes are recognized.² In cattle and sheep, serotypes 1 and 4 are the important pathogens.

Listeria monocytogenes is a common cause of morbidity in a variety of animal species, particularly sheep and also cattle, goats, and llamas. Three somewhat distinct disease patterns are recognized (and all occur in humans):

1. Septicemic disease with localization in the liver, spleen, and other viscera, particularly in young ruminants, pigs, rabbits, guinea pigs, chinchillas, and birds
 2. Metritis, placentitis, and abortion, especially in sheep and cattle
 3. Meningoencephalitis, seen most frequently in sheep, goats, and cattle and sporadically in other animals
- Episodes of disease within a flock tend to occur as one

of these three patterns. However, these syndromes are not mutually exclusive; for example, in attempts to reproduce the localized brain stem encephalitis by peripheral inoculation with the organism, a few animals will develop a bacteremic stage. Rare episodes of listerial myelitis have also been recorded in sheep.³

Listerial meningoencephalitis is a common endemic problem in sheep, cattle, and goats. On the basis of one characteristic clinical feature, it was designated circling disease by Gill in New Zealand in the 1930s. An association of this encephalitis with the feeding of corn or grass silage to stock has been recognized,^{4,5} probably for at least 60 years. Survival of the organism is less favored at low pH. In poor-quality silage in which the pH reaches 5 or higher, the organism replicates abundantly. Meningoencephalitis may occur as a flock problem in sheep and goats, whereas single cases are the rule in cattle herds.^{6,7} A seasonal pattern is noted, with most cases in late winter and early spring. In part, this may reflect animals housed through the winter and fed silage, but cases occur frequently at pasture also.

Clinical signs reflect brain stem injury and are similar in sheep, cattle, and goats. Affected animals are usually adults, but young lambs and goats have been affected.⁸ There is initially some depression, and affected sheep may stand separated from the flock. A propulsive gait develops, typically with continuous circling to one side or the other. Paresis of the masseter muscles impedes mastication. There may be a head tilt, torticollis, and spontaneous nystagmus. Facial nerve paralysis is reflected by a drooping ear, ptosis, lack of tone in the lips, and sometimes by exposure keratitis. Dysphagia develops, with drooling of saliva and prolonged retention of food in the mouth. Deficits progress in a few days to ataxia and paresis, followed by recumbency; death then ensues quite quickly. The CSF findings are helpful, with considerable elevations of protein levels and a pleocytosis predominantly of mononuclear cells.⁷ A presumptive antemortem clinical diagnosis is usually possible, and treatment with high doses of penicillin may be rewarding.

In cases that come to necropsy, there may be gross changes on the transverse sections of pons and medulla. These consist of yellowish tan foci that may be soft (malacia). The microscopic hallmark of this infection is a meningoencephalitis centered in the pons and medulla oblongata, particularly the nucleus and spinal tract of the trigeminal nerve and the trapezoid body. As viewed in transverse sections of the brain stem, these lesions are asymmetrical, favoring the side of the cranial nerve deficits. Inflammation tapers off rostrally and caudally, typically extending from the thalamus to the cervical spinal cord.

Inflammation in the degenerate neuroparenchyma (Fig. 3-32, A and B) is marked by prominent perivascular cuffs of inflammatory cells that include lymphocytes, monocytes, plasma cells, and fewer neutrophils; on occasion, eosinophils are present also. Similar populations are found in the

leptomeninges adjacent to areas of parenchymal injury and in lower numbers elsewhere. Typically the inflammation is a mixture of nonsuppurative and suppurative patterns. Inflammatory cells percolate through the neuropil, where they are admixed with reactive astrocytes and microglial cells. There is necrosis of individual neurons with intense cytoplasmic eosinophilia, as well as neuronophagia with neutrophils infiltrating the tattered perikaryon.⁹ Areas of malacia with gitter cells filling sites of liquefied parenchyma are common. Characteristic of listerial encephalitis is the formation of microabscesses; the gram-positive organisms can be demonstrated within such foci as well as within neutrophils, macrophages, and neurons.

Studies of the spontaneous disease in sheep⁹ have shown that neuritis of cranial nerves and ganglia, particularly the trigeminal, is common. Variably sized infiltrates of lymphocytes, macrophages, and neutrophils are found within nerve fascicles and their perineurial sheath. Massive influx into the ganglia may be associated with neuronal degeneration and Wallerian degeneration in proximal and distal segments of the nerve. The former may extend into the medulla in the spinal tract of the trigeminal nerve.

A postmortem diagnosis can be made by demonstrating the organism in the brain stem and trigeminal ganglion and nerve by immunofluorescent or immunohistochemical techniques (Fig. 3-32, C)^{10,11} and by isolation from the CNS, which is often aided by prior storage at 4°C.

Listerial meningoencephalitis is recorded sporadically in other species including pigs,¹² horses, dogs, and even giraffes.¹³ In humans it is sometimes acquired from eating contaminated cheese^{14,15} and turkey franks. Pontomedullary localization is also characteristic of the human infection.

The pathogenesis of the rhombencephalitis produced by *L. monocytogenes* has intrigued clinicians and pathologists for decades. Based on the constant topography of the encephalitis, largely restricted to the brain stem, most investigators have not favored the hypothesis that the organism takes a hematogenous pathway to the brain. A corollary to this statement is that experimental studies, which have employed intravascular or intracranial routes of inoculation,^{6,16} have induced a diffuse rather than a localized encephalitis. Instead, a route from the craniofacial tissues along the fifth and/or seventh cranial nerves has been proposed. Support for such a scenario can be found in natural and experimental cases of listeriosis in the asymmetry of brain stem and trigeminal nerve involvement. Furthermore, inflammation may be heavy in one branch of an affected trigeminal nerve and spotty in others, favoring the interpretation of ascending infection rather than centrifugal spread from brain stem to nerve. This does not deny that centrifugal spread—from the pons and medulla into the fascicles of other cranial nerves—may possibly occur.

The organism has been demonstrated within axons of cranial nerves by light⁹ and electron microscopy¹⁰ and centrally within neurons by electron microscopic examination.¹⁷

Inoculation is thought to occur into the buccal mucosa through abrasion or when teeth erupt, into an abraded nasal mucosa, or perhaps via accidental intraconjunctival installation such as with particles of silage. Interestingly, Olafson⁶ has commented that in sheep a catarrhal rhinitis may precede the development of encephalitis. Successful induction of brain stem infection in mice and goats has been achieved by administering the organism with abrasive foodstuffs.¹⁶ Experimental evidence in favor of centripetal spread has come from Barlow and McGorum,¹⁸ who employed a novel protocol, inoculating the microbe into tooth pulp. Brain stem

encephalitis was ipsilateral to the inoculated side or, if bilateral, was worse on the injected side.

Many aspects of the pathogenesis of this infection remain to be elucidated. After breaching the mucosal barrier, how the bacillus enters the nerve fiber and subsequently is transported along the axon is unknown. Assuming this pathway, it must also be asked how the organism incites an inflammatory response both peripherally within the nerve fascicle and centrally at its final destination within the brain stem.

References are on page 179.

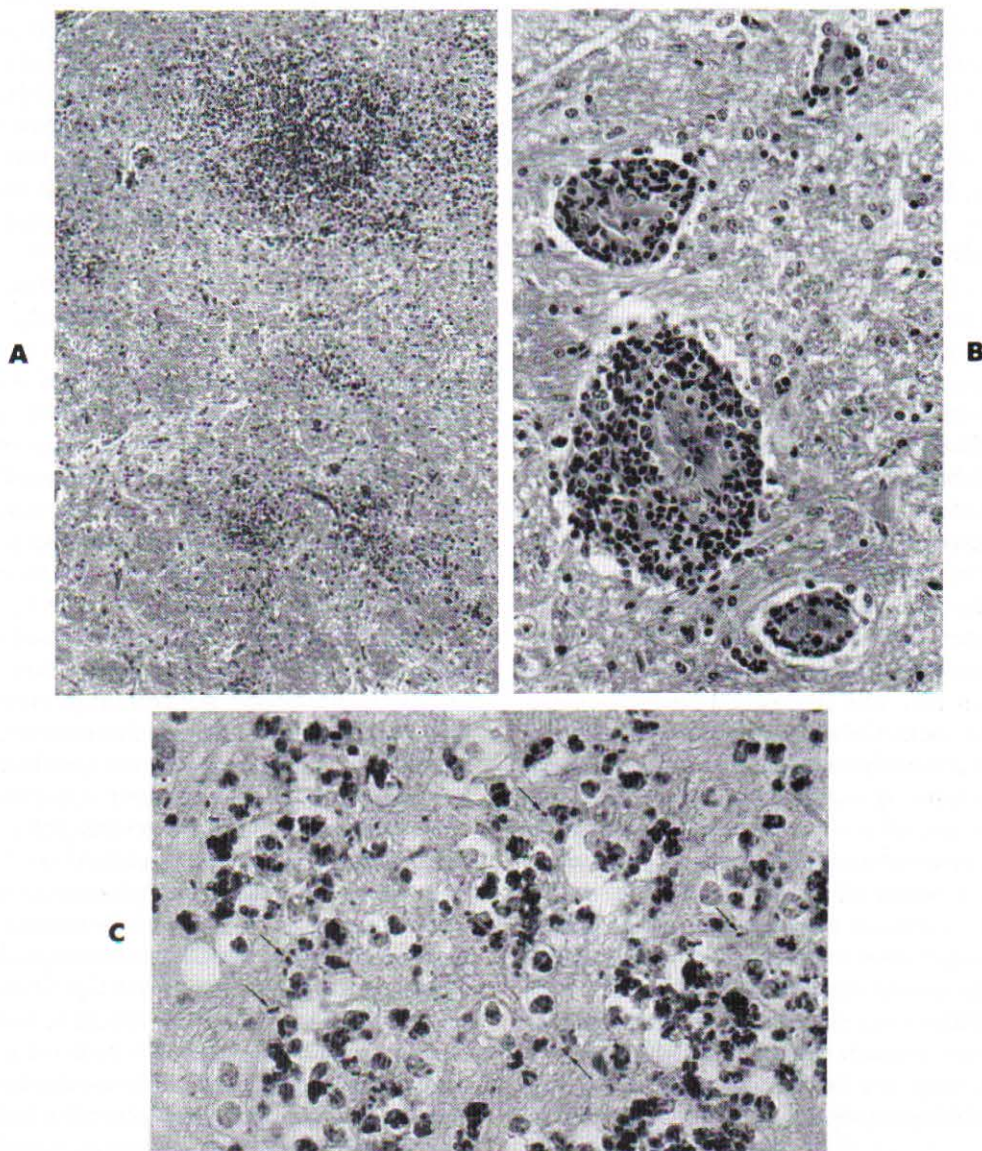


Fig. 3-32. Listeriosis. **A**, Foci of supuration in brain stem, lamb. (H&E, $\times 140$.) **B**, Perivascular cuffing. Mononuclear cells predominate, lamb. (H&E, $\times 350$.) **C**, Immunocytochemical demonstration of *Listeria monocytogenes* within neutrophils and free in the tissue (arrows) in a llama with listerial encephalitis. ($\times 560$.)

SCRAPIE AND THE TRANSMISSIBLE ENCEPHALOPATHIES

Scrapie

Transmissible mink encephalopathy

Bovine spongiform encephalopathy

Chronic wasting disease

Human spongiform encephalopathies

Scrapie is the prototype of a number of novel neurological diseases of animals and humans. The scrapie agent does not provoke an inflammatory response when it enters the CNS (or other tissues). Despite this fact, we have chosen to include these diseases in this chapter on the basis of their presumed infectious nature and their transmissibility to a variety of animal species. As a group, they are sometimes referred to as the transmissible spongiform encephalopathies; the degree of spongiform change induced is widely variable, however, especially when scrapie strains are compared in laboratory rodents.

Scrapie is a natural disease of sheep and, rarely, of goats. Its occurrence has been recorded since at least the middle of the eighteenth century, and the disease remains endemic in England, continental Europe, the United States, and elsewhere where sheep are raised.¹ The prolonged incubation period and unknown aspects of its epidemiology render absolute control difficult, although policies of slaughter and eradication and of breeding for resistance have some effect on the frequency of clinical disease.

In almost all aspects, scrapie and the scrapie agent are unusual. The clinical disorder in sheep occurs in adults, rarely under 2 years of age, often between 3 and 5 years, and sometimes later. It seems that infection is most commonly spread from ewes to their lambs before weaning,² and the incubation period is at least 2 years. The initial clinical signs may include alterations in behavior, ataxia, or pruritus. Hyperesthesia is common, with intermittent episodes of nervous behavior and trembling. Seizures may be precipitated by excitement or handling.³ Pruritus soon follows, with progressing severity. This is thought to represent an apparent development of cutaneous paresthesia that causes the sheep to rub and excoriate their fleece against any convenient object such as a fencepost. This constant scraping gives the disease its name in English and results in large areas of fleece loss. Sometimes this clinical feature is less apparent than is commonly believed. Affected sheep also bite at their wool and limbs. Scratching of the back often induces a nibbling movement of the lips with the head held high.

Affected sheep develop a stilted, trotting gait and progressive pelvic limb ataxia with proprioceptive loss. At rest there may be intermittent nodding of the head, muscle tremors, and a positional nystagmus. Some affected animals are

dysphagic, and blindness occurs also. Terminally there is anorexia and wasting to the point of emaciation, although some (e.g., Suffolks) may be fat; the clinical course lasts from a few months to a year.

Neuropathological changes in scrapie are microscopic, although the brain may be slightly shrunken. The definitive feature is vacuolation of gray matter, particularly neuronal populations symmetrically disposed along the brain stem and spinal cord. It is important to appreciate that neuronal vacuolation may be found in some brain nuclei, in some species, unrelated to the transmissible encephalopathies. However, the neuropathological changes and supporting clinical history usually permit a confident diagnosis, particularly by diagnosticians who routinely see this disease. The severity and distribution of degenerative changes are most marked in cases with a prolonged incubation period and pronounced clinical signs.⁴ The breed of sheep affected also has a bearing on the neuropathological findings; for example, Cheviot sheep have less neuronal vacuolation than other breeds. It is important to realize that the distribution, nature, and severity of CNS lesions are not random events but precisely controlled by the strain of the agent and genotype of the host.⁵

Vacuolation may occur in the neuronal perikaryon or neuritic processes. Within the cell body, there may be a single large vacuole or several smaller vacuoles. These vacuoles are empty and remain unstained with special dyes; sometimes they contain lightly eosinophilic, globular bodies. Vacuoles in the dendritic stems and axons impart an impression of sponginess to the neuropil (Fig. 3-33, A), often not clearly associated with a neuronal cell body. These changes, occurring diffusely, are found particularly in the lateral caudal portion of the reticular formation, the parasympathetic (dorsal) nucleus of the vagus nerve, and the lateral cuneate nucleus.⁶ Spongiform change is accompanied by astrocyte hypertrophy and proliferation. The astrocytosis varies from a modest reaction, most evident by increased numbers of paired astrocyte nuclei (and often more conspicuous with GFAP staining), to a marked proliferation. A very occasional perivascular cuff of mononuclear cells only emphasizes the fact that, in general, inflammatory changes are conspicuously lacking. Neuronal vacuolation, when severe, results in a Wallerian degeneration in ascending and descending tracts.⁷ Apart from the hallmark change of vacuolation, there are other forms of neuronal degeneration with shrinkage and hyperchromasia, a type of chromatolysis, and neuronal cell loss.⁴ A further change, occurring particularly in the cerebral and cerebellar cortices, unassociated with spongiform change, is cerebrovascular amyloid deposition (Fig. 3-33, B).⁸ Immunohistochemical studies suggest that this amyloid contains prion protein, probably formed from the host precursor protein.⁹ In murine models of scrapie, cerebral plaques containing an amyloid core may be produced.¹⁰

Ultrastructural studies of the neuronal pathology in nat-

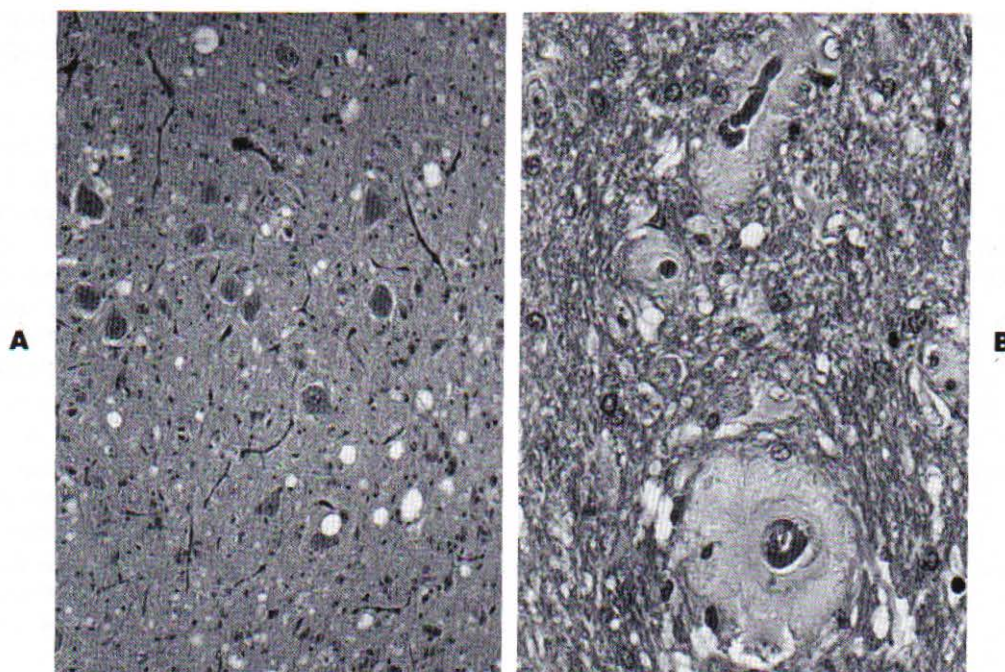


Fig. 3-33. Scrapie, sheep. **A**, Vacuolation and gliosis in parasympathetic nucleus of vagus nerve. (H&E, $\times 140$.) **B**, Cerebrovascular amyloid, cerebrum. (H&E, $\times 560$.)

ural and experimental scrapie and the other transmissible encephalopathies have revealed vacuoles bounded by single or double membranes within neuronal perikarya, dendrites, and axons.^{11,12} The vacuoles are largely empty apart from membranous debris or a finely granular material. Sometimes larger vacuoles appear to have formed by the coalescence of swellings in several processes.¹³ The genesis of this spongiform change is difficult to document; origins from mitochondria¹⁴ and from cisternae, such as the endoplasmic reticulum, have been suggested. In some models, swelling of astrocytic processes and ballooning of myelin sheaths occur also. Scrapie replication is probably a direct cause of neuronal vacuolation,² and it has been hypothesized that the agent forms within the lysosome, resulting in lysosomal leakage and subsequent spongiform cell change.¹⁵

The diagnosis of scrapie is routinely made on the basis of clinical and neuropathological findings. Transmission to other sheep or goats can be attempted but may require years to complete, whereas the incubation time in rodents is considerably shorter.¹⁶ The ultrastructural demonstration of **scrapie-associated fibrils (SAF)**,^{17,18} prepared from scrapie brain and revealed by negative staining, has diagnostic specificity for scrapie and the other transmissible encephalopathies. The SAF consist of two (sometimes four) twisted filaments, each 4 to 6 nm in diameter. These fibrils can be distinguished from other normal neuronal fibrils, but they quite closely resemble the fibrils of amyloid. Antibodies to SAF label amyloid deposits in scrapie brain,⁵ whereas the detection in lymphoid tissues of a glycoprotein component

of SAF may permit the preclinical diagnosis of scrapie.¹⁹ Immunoblotting for the proteinase-resistant form of prion protein has high diagnostic specificity and may be particularly valuable with autolysed specimens.²⁰ Immunohistochemistry is a further important aid to diagnosis.²¹

The morbidity rate for scrapie in a flock varies with the breed; once clinical signs develop, a fatal outcome is inevitable with very rare exceptions.²² In many ways this disease qualifies under Sigurdsson's category of slow virus diseases: a prolonged incubation, a single major target organ, and an invariably fatal outcome. However, unlike the virus of visna (the prototype of slow virus infection), the scrapie agent has most remarkable properties. It shows some resistance to boiling, to ultraviolet light and ionizing radiation, to ether, to nucleases, to cycles of thawing and freezing, and to strong formalin solutions that inactivate other agents. It is nonimmunogenic in the host, induces tissue changes that are degenerative rather than inflammatory, and cannot be isolated by routine tissue culture procedures. Furthermore, neural cells in tissue culture prepared from these diseases behave like transformed (neoplastic) cell lines.^{22,23}

Extensive studies with scrapie in mice have demonstrated that several distinct strains of the agent vary in their incubation time, virulence, and cytopathology.²⁴ Incubation time is also influenced by the dose and passage history of the inoculum. Equally, however, the importance of the host's genotype in the outcome of infection has been demonstrated. Breeds of sheep vary in their susceptibility to scrapie,²⁵ which, for example, occurs more frequently in Suffolk,

Leicester, and Cheviot breeds. Some scrapie-infected animals die of old age while still incubating the disease. The *sip* (scrapie incubation period gene) controls the incubation period in sheep;²⁶ the *sip* gene has two alleles of which that for susceptibility is dominant.

Scrapie can be transferred with various tissues and by a variety of routes. Intracerebral inoculation results in the shortest incubation period; a corollary of this statement is that the use of CNS tissue as the inoculum is the most reliable for transmission, although other tissues, including fetal membranes, will suffice. The placenta is a rich source of the agent and, together with the placental fluids, may be important in disseminating the agent in the field. Nasal and oropharyngeal secretions from the ewe could also harbor the agent.³ Experience with the natural disease suggests that the agent may be acquired at pasture, perhaps by ingestion. Early removal of lambs from a contaminated environment reduces the disease incidence. There may be vertical transmission from ewe to lamb, resulting in congenital infection, but positive evidence is lacking.²⁷ Some horizontal spread of infection between unrelated adults occurs.²⁸ Both the prolonged incubation period and lack of conventional immune responses in the host have made such epidemiological studies most difficult.

Following parenteral inoculation, the agent replicates first in lymphoid organs, particularly the spleen (splenectomy lengthens the incubation period), and then spreads to the CNS. Such studies in mice suggest that the agent passes by way of sympathetic nerves from the viscera to the spinal cord.^{29,30} Targeting lesions within the CNS, such as by intraocular inoculation, provides evidence of intra-axonal spread of the scrapie^{31,32} and Creutzfeldt-Jakob disease agents.³³ In nature there is no evidence of parenteral infection, and the enteric route is thought to be the natural pathway whereby the disease is acquired in sheep. In mice infected in this way, early replication occurs in the Peyer's patches (with lesser splenic involvement), and then the agent spreads, perhaps by the extrinsic nerves of the gastrointestinal tract, to the spinal cord.³⁴ During the replication in visceral tissues, the host is clinically normal. Once the agent gains access to the CNS, there is a lag phase, with local proliferation of the agent, and then the insidious development of clinical disease.

Extensive studies of murine scrapie have shown that the experimental disease can be varied by altering the mouse strain, the dose of the agent, the strain of the agent, and the route of inoculation. Murine scrapie incubation is also under genetic control, and the locus has been named the *sinc* gene for scrapie incubation. Recent studies have shown that the genes that control the scrapie incubation period in both mice and sheep are linked to the genes that encode the prion protein, a major component of SAF; in mice, these genes may be identical.³⁵ The prion is one model for the scrapie agent, of which the major protein is prion protein, PrP.³⁶

Scrapie was shown to be a transmissible disease in the 1930s,² and since that time the nature of the agent has puzzled and confounded investigators. This international debate, which at times has become quite heated, continues. Scrapie's resistance to procedures that denature conventional viruses (as described earlier) clearly shows that it has unique properties. Perhaps the prime question is whether the scrapie agent contains nucleic acid;³⁷ evidence for and against has been offered. Improved methods of purifying the infectious principle have associated infectivity with a low-molecular-weight protein (about 27 to 30 K). An association is also established between SAF and infection, and a major component of the SAF is also low-molecular-weight protein. Whether the SAF is the agent, or one form of it, or copurifies with the agent (which perhaps sticks to these fibrils) is still uncertain. A major constituent of the SAF is a sialoprotein PrP 27-30. This prion protein, encoded by a single gene, is conserved across a wide variety of animal species and is demonstrable in neurons³⁸ and glial, meningeal, and non-neural cells.³⁹ Levels of PrP mRNA in scrapie and control tissues are the same. Thus it is proposed that there is a post-translational modification of this normal protein in scrapie disease such that it accumulates as protease-resistant SAF and sometimes as extracellular amyloid.

Several models for the scrapie agent have been proposed.²⁴ The most conservative would be that scrapie is a very small conventional virus that contains nucleic acid and a protein component coded for by the agent. Prusiner's group⁴⁰⁻⁴² proposes the "prion" model, a proteinaceous infectious particle devoid of a nucleic acid element. If confirmed, this would be a revolutionary concept in microbiology. Predictably, this controversial hypothesis has generated the greatest criticism. In this hypothesis, the infecting agent would be the protease-resistant form of the prion protein, which is distinct from the normal cellular PrP. An alternative perspective⁴³ is that normal cellular PrP is the receptor for the as-yet unknown scrapie agent. Bruce and Dickinson have provided evidence that the scrapie agent has an independent genome.⁴⁴ They propose the "virino" model, wherein the particle has a small core of nucleic acid associated with a protein component that is host-derived, the latter fact accounting for the absence of an immunological response to the agent. Finally, Narang and associates have demonstrated abnormal tubulofilamentous structures from scrapie brain (and other spongiform encephalopathies) and provide evidence that they contain DNA.⁴⁵ Treatment of the tubules by proteolysis and nuclease releases filaments that resemble SAF. In experimental Creutzfeldt-Jakob disease and scrapie, the accumulation of these tubulovesicular structures in neuronal processes precedes the onset of clinical disease.⁴⁶

In the face of the accumulated knowledge of the properties of the scrapie agent, it is well to recall the arguments of Parry⁴⁷ that scrapie is an inherited disease arising by a "dual mechanism of gene and provirus" and, although trans-

missible, not naturally infectious. Analogies can be made with the Gerstmann-Sträussler syndrome of humans, a genetic disorder⁴⁸ with apparently autosomal dominant inheritance and yet transmissible to laboratory animals by inoculation of brain homogenates. It is still questioned whether naturally occurring scrapie is identical to the experimentally transmissible laboratory disease.²²

Scrapie also occurs naturally in **goats** but with much less frequency than in sheep. Disease is usually seen where goat herds cohabit with infected sheep. The neurological disorder, seen in 2-year-old or older goats, is marked by excitability, progressive pelvic limb ataxia with basewide stance, head tremor, and wasting.^{49,50} Some affected animals bite or rub at the coat but not to the extent that may be seen in sheep scrapie. Neuropathological changes are of neuronal degeneration (shrinkage and hyperchromasia or chromatolysis) and depletion, neuronal vacuolation, and astrogliosis.^{4,51} These lesions are most pronounced in the diencephalon, particularly thalamic nuclei, other brain stem nuclei, and cerebellar cortex. Such areas also harbor the highest titers of the agent.⁴⁹ Abundant multilocular vacuoles in neurons of the red nucleus may be prominent in goat scrapie. Caprine scrapie has been extensively studied by Pattison.²²

Transmissible mink encephalopathy

It is believed that the scrapie agent has entered several animal species beyond sheep and goats. **Transmissible mink encephalopathy** (TrME), first described in the United States in 1947⁵² and subsequently encountered in Finland, Germany, and the former Soviet Union, is a debilitating neurological disorder of adult, ranch-raised mink, characterized clinically by ataxia, progressive somnolence, debilitation, and death.⁵³ A classical spongiform encephalopathy (Fig. 3-34, A and B), most pronounced in the prosencephalon, develops in these animals after an incubation period of about 8 to 12 months. When CNS tissues from TrME-infected mink are inoculated into sheep and goats, disease is induced that clinically and pathologically is indistinguishable from scrapie.⁵⁴ Infected sheep products, fed to mink, are assumed to be the source, although this has not been established in all outbreaks. In one episode, sheep products were not fed, and the major source of animal protein was bovine, which raises the question whether there is a subclinical infection of cattle in the United States.⁵⁵ Spread from mink to mink may sometimes occur by cannibalism,⁵⁶ and infection from the feed probably involves both ingestion and intradermal inoculation, the latter resulting from fighting among young kits.⁵⁷ It appears that the passage of the scrapie agent through mink produces a change in the experimental host range; that TrME is scrapie seems almost certain,⁵⁸ but its source remains a matter of controversy.

Bovine spongiform encephalopathy

Wells and colleagues have reported a novel **bovine spongiform encephalopathy** (BSE) in the United Kingdom.⁵⁹

BSE occurs mainly in 3- to 6-year-old cattle, most often as single cases within a dairy herd. It is characterized clinically by apprehension, nervousness or aggression, truncal ataxia, hypermetria, and wasting.⁶⁰ Slaughter is usually necessary within 1 to 6 months. Neuropathological changes are characteristic of this group of diseases (Fig. 3-34, C) and are prominent in the parasympathetic (dorsal) nucleus of the vagus nerve, solitary tract nucleus, nucleus of the spinal tract of the trigeminal nerve,⁶¹ red nucleus (above normal background vacuolation in this nucleus), lateral vestibular nuclei, and the substantia gelatinosa of the spinal cord. The SAF have been demonstrated from BSE brain,⁶² most frequently in the basal nuclei and brain stem.⁶³ The experimental transmissibility of BSE to mice and cattle has been established.⁶⁴⁻⁶⁶ It is assumed that scrapie-infected ovine meat, rendered into meatmeal and bonemeal, was fed to British cattle,⁶⁷ which has resulted in many thousands of cases of BSE in dairy and a few beef herds across the United Kingdom. Early in the epidemic, recycling of BSE-infected cattle through the rendering process probably contributed also to the spread of BSE. Epidemiological studies determined that the first recorded case was in April 1985 and that contamination of cattle feed first occurred in 1981-1982. This time frame supports infection of most cases as calves.⁶⁷ In England, **spongiform encephalopathies**, similar to BSE, have been observed in a **nyala**, a **gemsbok**, an **eland**, an **arabian oryx**, and a **greater kudu** housed in wildlife parks or zoos.⁶⁸⁻⁷¹ In these cases, the agent may also have come from contaminated feed. A few **domestic cats** with a spongiform encephalopathy have also been recognized in Britain.^{72,73} The emergence of BSE has once again raised the issue of transmissibility of these diseases to humans.⁷⁴

Chronic wasting disease

A transmissible spongiform encephalopathy has been recognized in mule deer, black-tailed deer, and Rocky Mountain elk housed in wildlife facilities in Colorado and Wyoming.^{75,76} Affected animals, generally in the 3- to 5-year age range, run a chronic course for several months with an altered sensorium and behavioral abnormalities, progressive weight loss, depression, and ultimate demise. There is a spongiform encephalopathy with a distribution much like that of scrapie and BSE;⁷⁷ amyloid plaques have been found in some CNS lesions.⁷⁸ This **chronic wasting disease** of deer and elk is transmissible to other deer and to ferrets. The primary source of the agent (scrapie?) is not known.

Human spongiform encephalopathies

Finally, we must mention those examples of the transmissible encephalopathies that afflict humans.⁷⁹ **Kuru** is largely a syndrome of progressive cerebellar ataxia that was epidemic in the Fore natives of New Guinea. The disease was transmitted by the practice of cannibalism and with the decline of this custom is now disappearing.⁸⁰ **Creutzfeldt-Jakob disease**^{23,81} is a rare, subacute, progressive neuro-

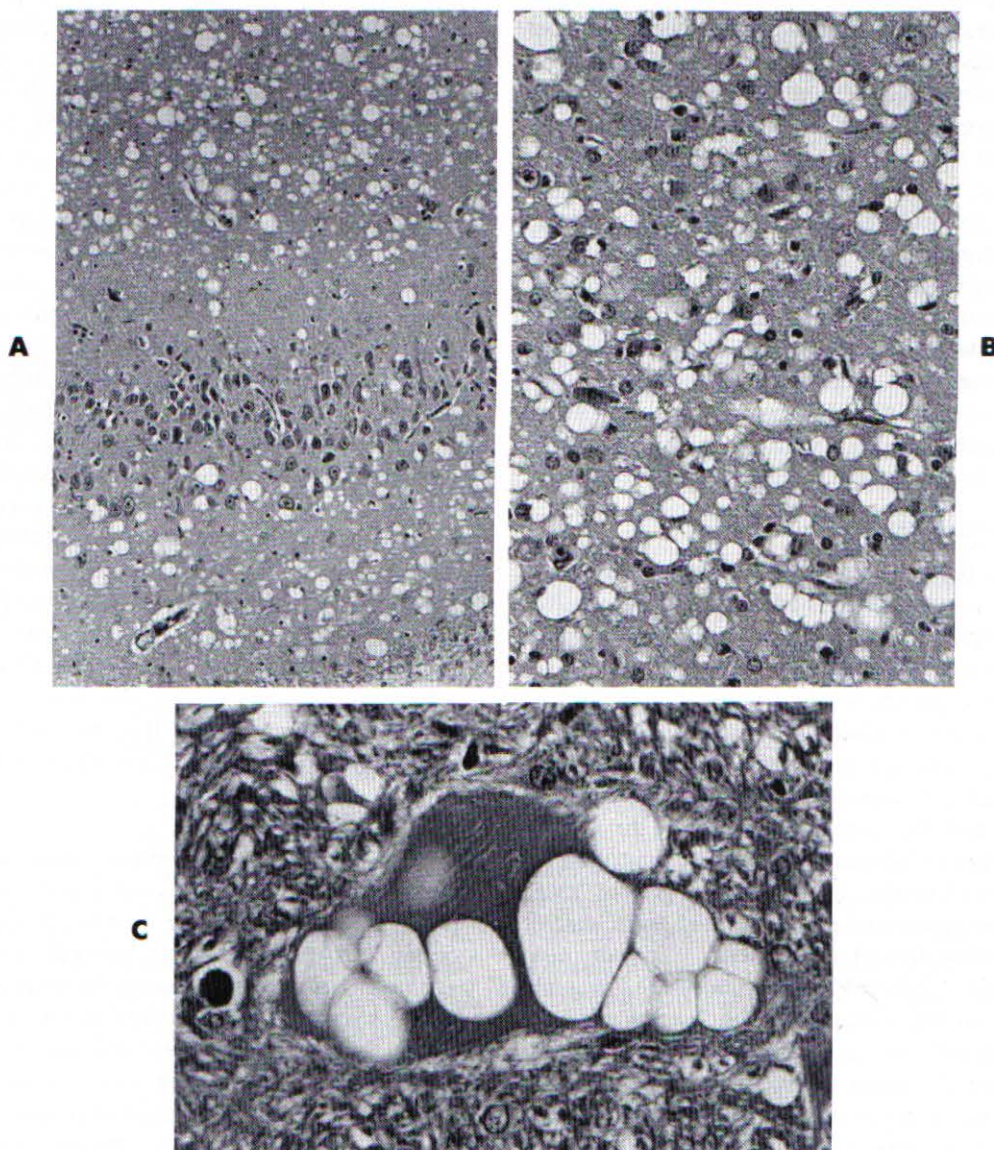


Fig. 3-34. A, Transmissible mink encephalopathy (TME). Spongy change in hippocampus. (H&E, $\times 140$.) B, TME, thalamus. (H&E, $\times 350$.) C, Bovine spongiform encephalopathy. Vacuoles in a neuron, medulla. (H&E, $\times 560$.)

logical disorder usually presenting between the fourth and sixth decades and characterized by dementia with pyramidal and extrapyramidal signs. Both diseases are marked by a spongiform encephalopathy and are transmissible to laboratory animals. **Gerstmann-Sträussler** syndrome is seemingly vertically transmitted as an autosomal dominant trait and is marked by spinocerebellar signs and subsequent dementia. Spongiform changes are less conspicuous, but amyloid plaques are abundant. In **fatal familial insomnia**, there is thalamic atrophy from neuronal loss and widespread spongiosis is uncommon.⁸²

References are on page 179.

BOVINE HERPESVIRUS MENINGOENCEPHALOMYELITIS

Herpesviruses are common pathogens of the respiratory tract and external genitalia of humans and animals. In cattle, such syndromes have been designated infectious bovine rhinotracheitis and vulvovaginitis. Sporadic, spontaneous episodes of a meningoencephalitis in calves have been associated with the bovine herpesvirus type 1,¹ and experimental infections with BHV 1 have been reported.^{2,3} Based on DNA restriction endonuclease analysis, some of the viral isolates from cases of encephalitis in calves resemble the classical BHV 1 (respiratory subtype), whereas other strains have different restriction patterns^{4,5} and constitute an encephalitic subtype. In the United States, nine BHV 1 isolates from the brains of calves or adult cattle were reported.⁶ Six animals lacked CNS lesions and had the respiratory subtype in the brain. Of three with encephalitis, two yielded the encephalitic and one the respiratory subtype.

Affected calves, usually under 6 months of age, are pyrexemic and may show abdominal pain, head pressing, circling, and violent seizure activity. The clinical course lasts about 4 to 7 days, and the mortality rate may be high. Macroscopic changes in the CNS are not found, but histological findings are a diffuse meningoencephalomyelitis. The reaction is nonsuppurative and involves the leptomeninges and neuroparenchyma at all levels. Perivascular lymphoid cuffs about blood vessels with swollen endothelia and microglial cell foci are found diffusely in gray and white matter of the brain and spinal cord. Neuronal necrosis, a hallmark of some herpesvirus encephalitides, is normally not prominent, but has been described in experimental infections.² Vasculitis, another feature of herpetic infections, has been recorded.⁷ In well-preserved specimens, acidophilic intranuclear inclusions are found in neurons and astrocytes. As is the custom of the herpesviruses, establishment of a ganglionitis and persistence within the craniospinal ganglia are to be anticipated. This has been demonstrated for this agent in the trigeminal ganglion of cattle,^{8,9} and virus may be reactivated with corticosteroids.^{10,11}

Studies by Bagust and Clark³ suggest that BHV 1 spreads from the nasopharynx by the maxillary and mandibular

branches of the trigeminal nerve to the pons with subsequent generalization. Intravenous inoculation with BHV 1 induces viremia but does not produce CNS infection.¹² In humans, herpes simplex virus is an important cause of encephalitis. Dissemination from the trigeminal ganglion, a known site of persistence, is envisaged.¹³

References are on page 181.

SPORADIC MENINGOENCEPHALOMYELITIS OF SWISS CATTLE

A sporadically occurring meningoencephalomyelitis of cattle in Switzerland was reported by Fankhauser in 1961.^{1,2} On clinical and pathological grounds, a distinction was made from sporadic bovine encephalomyelitis (also known as Buss disease), which is a chlamydial infection. That the Swiss disease is different has been supported by the isolation of a paramyxovirus from an affected cow.³

Although sporadic, this CNS disorder of Swiss cattle is not rare, and by 1976 more than 120 cases had been studied.⁴ Affected cattle are mainly between 1 and 4 years of age and usually occur as single cases within a herd. Clinical disease may progress rapidly, slowly over weeks to months, or follow a waxing and waning course.¹ Signs of neurological dysfunction include changes in sensorium and motor functions. Initial apathy may give way to aggressive, rabies-like behavior. There may be paralysis of the tongue, difficulty in swallowing, and hypersalivation. Sometimes signs of cerebellar dysfunction are prominent and correlate with severe cerebellar cortical inflammation and degeneration.² The CSF shows a mononuclear cell pleocytosis and positive globulin reaction.

The pathological findings are microscopic, widespread in the neuraxis, and somewhat variable in distribution from case to case. The midbrain and medulla are consistently affected. There is a lymphocytic and histiocytic meningitis, choroiditis, and encephalitis involving gray and white matter. Cells from perivascular cuffs mingle with reactive astrocytes and microglia, which form focal knots of cells and a diffusely hypercellular neuropil. Perivascular cuffs also contain a few plasma cells and an occasional eosinophil. Parenchymal damage is not pronounced, and there are no inclusion bodies to be found.

Fankhauser suggested that this encephalomyelitis may reflect a rare manifestation of a common viral infection of cattle; the Bachmann isolate³ may be the etiological agent. A cell-associated bovine morbillivirus has been isolated from U.S. cattle with malignant catarrhal fever⁵ but currently is not known to be a pathogen.

Diagnostic pathologists elsewhere, on occasion, encounter idiopathic nonsuppurative encephalitides in cattle (for example, Munday's experience in Australia⁶). Accordingly, this syndrome afflicting Swiss cattle may be more widespread than is generally appreciated.

References are on page 181.

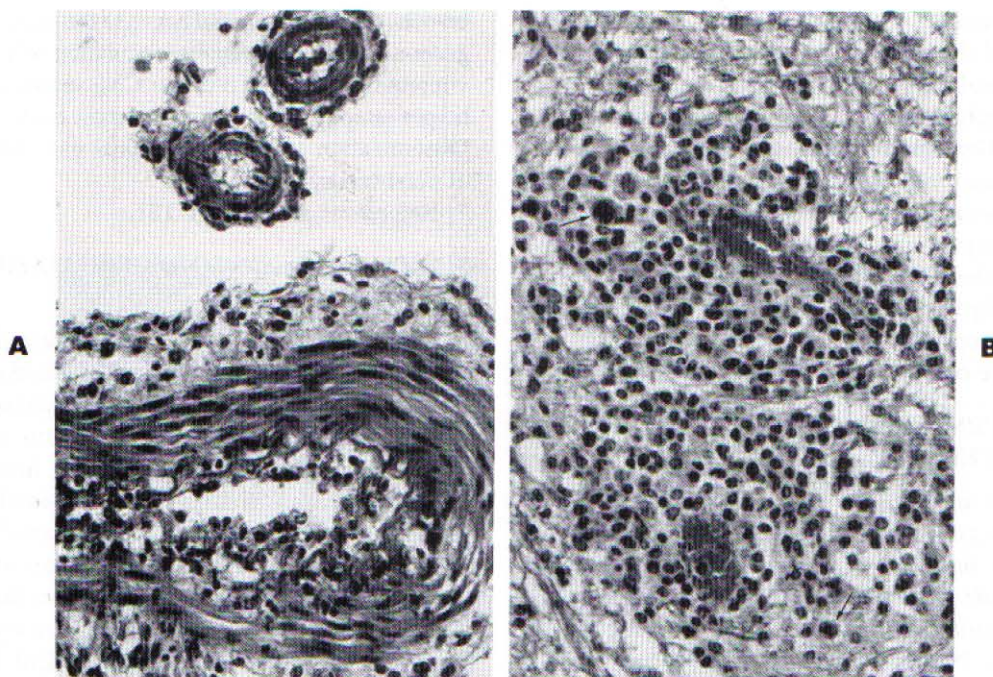


Fig. 3-35. Malignant catarrhal fever. A, Meningeal vasculitis, cow. (H&E, $\times 350$.) B, Lymphocytic vasculitis, medulla, deer. Note occasional binucleate cells (arrows). (H&E, $\times 140$.)

MALIGNANT CATARRHAL FEVER

Malignant catarrhal fever (MCF) is a disease of cattle, deer, and sporadically other ungulates. The condition is best known in cattle and occurs in two geographical forms that are clinically and pathologically very similar to each other. The African form of MCF is caused by an alcelaphine herpesvirus (AHV-1) that is carried and shed by wildebeest.¹ In other countries, MCF occurs in cattle exposed to sheep and is caused by an unknown agent, presumably carried and disseminated by sheep. Several viruses have been isolated from cattle with sheep-associated MCF, such as bovine syncytial virus and a morbillivirus,² but such agents have failed to fulfill Koch's postulates. Immunological evidence suggests that the alcelaphine herpesvirus and the sheep-associated agent are antigenically related,³ and it seems highly likely that the non-African form of MCF is caused by a herpesvirus prevalent in sheep.^{4,5}

Episodes of **MCF in cattle** tend to be sporadic, but, for unknown reasons, epidemics occasionally occur;⁶ invariably the mortality rate is high. Some flocks of sheep transmit the agent to cattle more efficiently than others, but what factors predispose cattle and deer to becoming infected is unclear.⁴ The clinical course of MCF can vary from peracute through acute to chronic forms. In a "typical" case there is high fever, depression, profuse salivation, nasal discharge, corneal opacity, dyspnea, and diarrhea. Clinical neurological signs, which develop late in the course of the disease, are nonlocalizing and include lethargy, ataxia, and terminal sei-

zures. At necropsy there are erosive or ulcerative lesions in the gastrointestinal and respiratory tracts. Lymph nodes are enlarged, and there is a considerable lymphoid hyperplasia. Pathognomonic of MCF is a lymphocytic vasculitis⁷ with fibrinoid necrosis of arteries and arterioles in many organs. The CNS lesions are microscopic and reflect this disseminated vasculitis, which affects parenchymal and meningeal blood vessels (Fig. 3-35, A). Large and small lymphocytes and histiocytes infiltrate the tunica adventitia and media of neuraxial arteries and spill into the perivascular tissues. Degenerative changes in neural tissue and reactive gliosis are patchy and only mild, such that the microscopic lesion is readily identified as a primary vasculitis rather than an encephalomyelitis. The parenchymal and meningeal involvement is directly related to the vascular lesion. Fibrinoid necrosis of blood vessels in the CNS is less common than in the lymph nodes, kidneys, adrenal glands, and other visceral organs.

Malignant catarrhal fever, particularly the African form, is transmissible to rabbits and has been studied extensively in this species.⁸⁻¹⁰ Hybridization techniques can identify the DNA of AHV-1 and doubtless will have diagnostic applications.^{11,12} MCF has emerged as an economically important disease of **farmed deer** (Fig. 3-35, B) in Scotland, Australia, and New Zealand.^{13,14} It is sporadically observed in a wide range of other free-living and captive ruminants, including buffalo, bison, and moose.^{15,16}

The pathogenesis of this fascinating disorder remains un-

certain. The presence of vasculitis as the cardinal feature has been taken as evidence that MCF is a virus-induced immunopathological disorder. Injury to epithelial tissues in many organs is a second consistent observation and follows an infiltration of epitheliotropic lymphoid cells, reminiscent of the change in contact hypersensitivity and graft-versus-host disease.¹⁷ Reid and associates¹⁸ have hypothesized that in MCF the crucial event is viral infection and subsequent dysregulation of large granular lymphocytes. Loss of their suppressor cell activities would facilitate the (benign) T cell proliferation, prominent in lymphoid organs, while the unchecked natural killer cell activity could mediate tissue destruction.

There are some interesting parallels between MCF and human infectious mononucleosis. Mononucleosis is also caused by a herpesvirus (Epstein-Barr virus) and is an acute although usually self-limiting disorder. This disease, too, is marked by lymphoproliferative changes in lymphoid organs and the presence of atypical lymphocytes in circulation.

References are on page 181.

THROMBOTIC MENINGOENCEPHALITIS OF CATTLE

Haemophilus somnus, the cause of thrombotic meningoencephalitis (TME), is an important bovine pathogen, particularly in Canada and the United States. The organism responsible is a small, gram-negative coccobacillus. Classification of this agent is not secure, and assignment to another genus seems possible. Close similarities, if not identity, between *H. somnus* and the ovine pathogens *H. agni* and *Histophilus ovis* have been proposed.¹

Haemophilus somnus is the cause of a peracute to acute, septicemic infection of cattle. The organism also produces a fibrinous pneumonia in calves and endometritis-vaginitis in cattle. Septicemic disease with widespread vasculitis and TME is primarily a disease of beef cattle maintained in feedlots; episodes have occurred in dairy breeds at pasture. Affected cattle are typically around yearling age, with most cases in the early winter months.² In an outbreak, the first sign that all is not well may be cattle found dead or recumbent and moribund. Coma and death ensue rapidly. If the infection is less fulminating, there is pyrexia, stiffness, reluctance to move, sometimes cough and tachypnea, and a spectrum of neurological signs reflecting the potential for diffuse involvement in the CNS. Affected cattle may be depressed or irritable and may circle with an ataxic/paretic gait. Some may be blind. Recumbent cattle may show opisthotonus, and seizures can occur terminally. The differential diagnosis includes lead poisoning and polioencephalomalacia.³ Neurological deficits may be asymmetrical (e.g., unilateral blindness¹), which would not be anticipated with lead toxicity or thiamine deficiency. The CSF contains many cells, mostly neutrophils, elevated levels of protein, and depressed glucose levels. Attempts to isolate *H. somnus* from CSF are often negative.

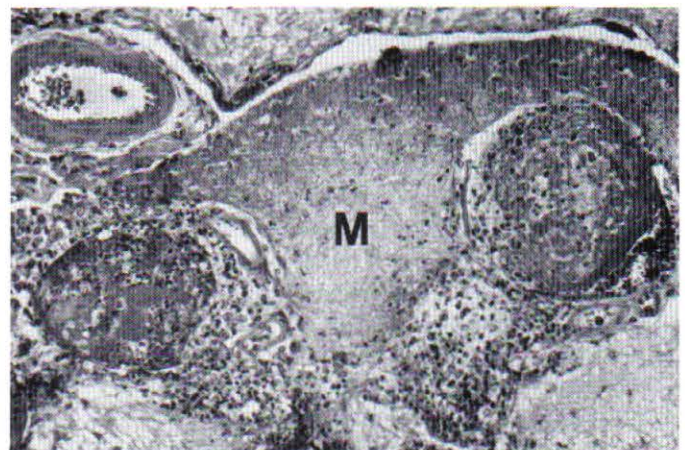


Fig. 3-36. Thrombotic meningoencephalitis, cow. **A**, Hemorrhagic lesion in lentiform nucleus. **B**, Vasculitis, thrombosis and fibrinous exudation in the meninges (*M*), cerebrum. (H&E, $\times 225$.)

At necropsy, there are hemorrhagic infarcts in the brain and spinal cord, myocardium, and skeletal muscles and a fibrinopurulent serositis, arthritis, and synovitis. The brain is swollen with flattened gyri and contains soft, red-brown hemorrhagic foci (Fig. 3-36, *A*), some reaching 4 cm in diameter; similar foci are found in the spinal cord. Fibrinopurulent meningitis is common, frequently involving the spinal leptomeninges. Microscopic examination of such lesions reveals a septic vasculitis (Fig. 3-36, *B*) with thrombosis of meningeal and parenchymal blood vessels; bacterial colonies are often evident. There is necrosis of the vessel wall and an intense local neutrophilic response. Areas of ischemia in the adjacent neuroparenchyma may be pale-

staining with pyknotic remains of glial nuclei, or they may be hemorrhagic. Bacterial colonies invade from the vessel wall into the infarcted tissue. A diagnosis can be established by bacterial isolation from the brain (most reliable), heart, kidney, lung, and elsewhere.⁴

Fibrin thrombi are consistently found in blood vessels in other organs such as the lung, liver, and kidney and disseminated intravascular coagulation (DIC) may be precipitated.⁴ However, the pathogenesis of this form of *H. somnus* infection appears to involve primary vascular endothelial injury, perhaps mediated by a bacterial toxin.¹ In arterial explant cultures, *H. somnus* attached to endothelial cells, which rounded up and separated, exposing subendothelial collagen;⁵ in vivo such would result in local coagulation. Thus to what degree there is bacterial-induced thrombosis on one hand and nonspecific DIC on the other is a moot point. The earlier designation of this disease as thromboembolic meningoencephalitis (TEME) has been modified to TME in the absence of clear evidence of embolic phenomena.

Many questions remain regarding the epidemiology of the agent and the pathogenesis of the acute infection. Infection in many cattle seems to occur subclinically, as judged by serology, with episodes of septicemia, TME, and death precipitated by cold weather, transportation, and/or crowding of animals.^{4,6} Strain differences in the organism may also exist, some being encephalopathic, whereas others are associated more with fibrinous pneumonia in calves or reproductive tract infection in adult cattle.

Histophilus ovis has been recognized as a cause of suppurative meningoencephalitis in sheep.⁷

References are on page 181.

SPORADIC BOVINE ENCEPHALOMYELITIS

Sporadic bovine encephalomyelitis (SBE), also known as Buss disease, was identified as a specific polyserositis and encephalomyelitis of cattle by McNutt and Waller in 1940.¹ This disease is now recognized in Australia, Japan, the former Czechoslovakia, and Hungary, and it probably occurs elsewhere. The etiologic agent is a chlamydia; in many early reports, the older designation of psittacosis-lymphogranuloma venereum group is used.

As the name implies, the condition is sporadic, often affecting only a few animals in a herd. All age groups are susceptible, calves more so than adults. Clinical signs begin abruptly with fever, depression, anorexia, drooling saliva, and nasal discharge.² This progresses to a syndrome of difficulty in walking, stiffness, knuckling of the fetlocks, staggering, and collapse. Moribund calves die in a few days. Some, depressed and emaciated, slowly recover.

At necropsy, there is a polyserositis and a meningoencephalomyelitis.³ The serositis is serofibrinous and may affect the peritoneum, pleura, pericardium, joint spaces, and tendon sheaths. Peritoneal involvement is most consistent. Gross brain findings are of moderate edema and congestion.

Microscopically, there is an exudative meningitis, particularly pronounced on the ventral surface of the brain stem. Encephalomyelitis is disseminated from the cerebral cortex to the lumbar spinal cord. Infiltrates consist of mixed lymphoplasmacytic and neutrophilic leukocytes and involve all elements. Degeneration and necrosis in gray matter may be severe. Vasculitis is seen, with swollen, reactive endothelia and mixed leukocytic infiltrates within the adventitia. Focal malacic areas, which are observed, may have a vascular basis.

Chlamydial elementary bodies (the initial intracellular developmental stage of the organism) occur in the cellular exudate at inflamed surfaces, and the diagnosis can be confirmed by guinea pig and egg inoculation.

References are on page 182.

EQUINE VIRAL ENCEPHALOMYELITIS

A variety of viral agents, including rabies virus and the unclassified Borna disease agent, cause encephalomyelitis in the horse. In this section, we shall discuss the arthropod-borne viruses that, on occasion, produce neurological disease in the horse, other equidae, and other vertebrates, including humans. Three diseases are of greatest importance: **Eastern, Western, and Venezuelan encephalomyelitis** (EE, WE, and VE). These agents are members of the *Alphavirus* genus; epidemics of this viral encephalomyelitis in horses have been recorded since the last century. Episodes of CNS infection occur in North, Central, and South America, predominantly involving the United States, Caribbean area, and the northern parts of South America. In the United States, EE and WE are the endemic diseases, but VE has entered from South America.

Transmission of these alphaviruses is by insect vectors, chiefly mosquitoes;¹ therefore, clinical disease is seen in mid to late summer months, when these insects are most active. In tropical climates, however, the disease incidence may be less seasonal. Furthermore, with the rapid movement of horses across the country for racing and other competitions, horses incubating the infection may be presented in states where EE or WE is infrequently encountered.

Clinically, WE, EE, and VE are similar and cannot be differentiated by physical examination.² Some infections are probably inapparent with nothing more than mild fever and seroconversion. Other horses show systemic illness, reflected by fever, leukopenia, depression, tachycardia, loss of appetite, and sometimes diarrhea.³ In some infected horses, CNS invasion occurs, but what determines when it will happen is not entirely clear; one factor is the specific agent in question (EE, WE, or VE). The route of viral entry into the brain is uncertain. Viremia with subsequent invasion across CNS vascular endothelium has long been proposed, but for only some agents has endothelial infection been demonstrable. Studies with cultured mouse brain endothelium have shown differences in permissiveness for alphaviruses and flaviviruses.⁴ Further, some viruses show po-

larity in their release from endothelial cells, whether from luminal or abluminal surfaces, which may be important in neuroinvasion. The case has also been made for CNS infection along neurons from the olfactory epithelium rather than the hematogenous route.⁵ Thus immune events in the nasal mucosa may have a crucial bearing on progression of the infection to the CNS.

Neurological disease primarily reflects damage to cerebrocortical tissue, which bears the brunt of the viral injury. Changes in sensorium are conspicuous; initially there may be hyperexcitability and restlessness, but this soon leads to somnolence and severe depression. There is cortical blindness, and affected horses may be propulsive, circle, and head press. The course is often brief (1 or 2 days), with ataxia and paresis leading to recumbency. These animals may thrash violently when recumbent, leading to significant self-injury. Some affected horses do not become recumbent and survive, but are lethargic ("dummies") from their cerebrocortical injury. In some cases, the early signs may pass undetected, and apparently healthy horses are found dead.⁶ A peracute course is more typical of EE and VE; WE is often subacute.

Leukocytosis commonly occurs in the CSF, which is initially neutrophilic, especially with EE. The fluid is often xanthochromic and has elevated protein. Occasionally a prominent eosinophilic pleocytosis occurs in EE.⁷ At necropsy, there are no gross lesions. Microscopic changes predominate in gray matter and, although diffuse in the brain, are most marked in the cerebral cortices, thalamus and hypothalamus, and are milder at more caudal levels. In horses that die acutely, venules with swollen endothelium are cuffed with polymorphonuclear leukocytes that percolate into the neuropil (Fig. 3-37). Vascular necrosis and thrombosis are prominent in some cases. In EE the response remains largely neutrophilic, in VE it is a mixture of neutrophils and lymphocytes, while WE shows a more non-suppurative inflammatory response. In fulminating cases in which the predominant inflammatory cell is the neutrophil, a characteristic feature is necrosis and fragmentation of these leukocytes.⁸ Gliosis, both focal and diffuse, is of microglial type. There may be small areas of malacia and liquefaction, filled with gitter cells.⁹

Diagnosis is made on the basis of clinical suspicion and compatible histopathological findings. Attempts to isolate virus from the brain are often unrewarding unless the course is peracute. Viral antigen has been demonstrated by immunofluorescent technique,¹⁰ and immunocytochemical methods may be equally or more satisfactory. A single serum sample may offer a presumptive diagnosis of WE in unvaccinated horses,¹¹ as the neurological disease follows the systemic phase, during which antiviral immune responses are triggered. Often it is impossible to obtain paired sera because of the fulminating course. If available, a fourfold increase in titer is considered to be diagnostic.

The EE, WE, and VE are related but distinct alphaviruses. With around 40% mortality, WE is least virulent for

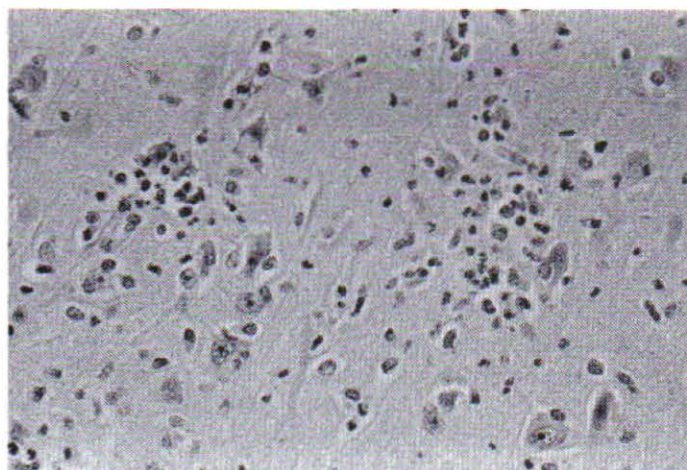


Fig. 3-37. Eastern equine encephalomyelitis, horse. Two foci of neuronal degeneration and neutrophilic influx, cerebrum. (H&E, $\times 350$.)

the horse. In contrast, EE and especially VE are lethal in up to 90% of cases. Susceptibility is higher in young horses (and children).

In endemically infected areas WE and EE are maintained by a wild bird (reservoir)—mosquito (vector) cycle, particularly in swampy or tropical areas.¹² These avian reservoirs have a sufficiently high viremia to permit infection of mosquitoes and so maintain the disease. In wild birds indigenous to North America, the infection is innocuous, whereas in non-native birds such as pheasants, starlings, and sparrows the disease is lethal. Infection of horses and humans¹³ occurs with the movement of virus from the swamp, carried by reservoirs, vectors, or both. Certain wild birds and mosquitoes (*Culiseta*, *Culex*) are most important in maintaining the endemic infection, whereas the same or other vectors are involved in the spread to horses and humans, for example, *Aedes* mosquitoes that will feed on non-avian hosts.¹⁴ On occasion, encephalomyelitis is seen in cattle and pigs¹⁵⁻¹⁷ and other species. Infection in many vertebrates is "dead end" in that further transmission (from that case) is not possible. This probably pertains to horses infected with the EE virus. Depending on the virus in question, however, some animals may act as "amplifiers," attaining high levels of viremia as occurs in infected birds.

EE occurs mainly along the Atlantic and Gulf coasts of North America and in the Caribbean, and WE to the west of the Mississippi; some overlap does occur. Both spread through Central into South America. In Venezuela, Brazil, Argentina, Central America, and Mexico, VE is important, and it differs from EE and WE in that, although birds may be infected and play a role in transmission, rodents are the prime virus reservoir. The VE virus is divided into subtypes: Subtype 1 infects horses and humans, and the others are purely rodent viruses. Although mosquitoes are the prime vector, ticks and other ectoparasites are incriminated. For

VE, susceptible horses are amplifier and not dead-end hosts, and in an epidemic mosquitoes can transmit the virus from horse to horse.³

Japanese encephalitis, caused by a flavivirus, is an important human disease in China, Korea, and Japan, with episodes of high mortality. Transmitted by *Culex* mosquitoes, the reservoir avian hosts are unknown. Horses and donkeys develop encephalitis, and this attains importance in Japan. Other livestock show evidence of infection but not disease.¹⁸ In pregnant pigs, however, reproductive losses occur, and encephalitis is seen in the first months of life. Swine are important because they are amplifier hosts.³

Other arboviruses that are known or may prove to cause equine encephalomyelitis are **West Nile virus**,³ **Semliki Forest virus**, **louping ill virus**,¹⁹ **Murray Valley encephalitis virus**,²⁰ **Near Eastern equine encephalomyelitis virus**,²¹ **Powassan**,²² **snowshoe hare virus**,²³ and **Main Drain virus**.²⁴ **LaCrosse virus** has been recognized as a cause of necrotizing meningoencephalitis in dogs.²⁵

References are on page 182.

EQUINE HERPESVIRUS 1 ENCEPHALOMYELOPATHY

Equine herpesvirus type 1 (EHV-1) is the cause of respiratory tract infection, abortion, and CNS disease in the horse. Neurological disease may occur as the primary disorder or may follow rhinopneumonitis or abortion in the affected horse or, commonly, other in-contact horses.¹ Horses of all ages are susceptible, and episodes seem to occur more frequently in some years than in others.²

Signs of CNS disease are of abrupt onset, and horses may be found recumbent as the first evidence of disease.³ Clinical signs most often reflect spinal cord lesions; ataxia and paresis of the pelvic limbs are common, and passive dribbling of urine is a characteristic feature. Signs may be mild and transient as recovery or compensation occurs with minimal lesions. With severe lesions, recumbency occurs in 12 to 24 hours from the onset of neurological signs. Sometimes ascending paralysis is observed. The CSF from affected horses is often xanthochromic⁴ with elevated protein but normal numbers of cells (i.e., virtually none). During the early stage of the infection, there is a cell-associated viremia, and virus may be isolated from the buffy coat in affected horses. Failure to isolate EHV-1 does not rule out the diagnosis, however, especially in the neurological form of the disease.² Diagnosis can be supported if initially the serum antibody titer is significantly elevated or confirmed if, on a second serum sample 2 or more weeks later, there is a twofold to fourfold increase in titer. Vaccinated horses are not immune to this form of the disease.

At necropsy, hemorrhagic foci are found throughout the brain and spinal cord⁵ or focal areas of yellow to tan discoloration of preserved tissue. Those in the cord may show a linear radiating pattern from the surface into the white matter, related to their distribution about blood vessels (Fig.

3-38). Microscopic findings are a vasculitis⁶ with secondary injury to the neuroparenchyma. Affected arteries and venules are found in the leptomeninges, brain, spinal cord, and spinal ganglia. In peracute disease, vascular thrombosis is found but vasculitis, affecting particularly the tunica adventitia and media, is more common. Inflammatory cells in the vessel wall are mostly mononuclear types; fibrinoid necrosis is uncommon. Syncytia formation in the tunica intima is described in experimental cases,⁷ but is rare in the natural disease. Capillaries and venules are often distended with erythrocytes and show degeneration with pyknosis of endothelia and mild perivascular cuffing. Parenchymal injury ranges from infarcts, which may be ischemic or hemorrhagic, to areas of less severe degeneration characterized by ballooning of myelin and concurrent axonal swelling. The latter pattern often is seen in the territory immediately around small injured vessels. In the brain, vascular lesions may be seen on the surface—in the cerebral cortex—and infarcts deeper in the cerebrum and brain stem. It is important to recognize that inflammatory events are directed to the target blood vessel; little leukocytic influx occurs into the damaged gray or white matter. Viral antigen can be demonstrated by immunofluorescent and immunocytochemical techniques.⁸

Pathogenesis studies of the neurological form of EHV-1 infection in the horse are few,⁷ as the CNS disease is difficult to reproduce.⁹ In natural cases, virus has been isolated from affected CNS tissues.^{1,8,10-12} The EHV-1 is classified into two subtypes: Both produce respiratory tract infection, but only subtype 1 consistently produces abortion and paresis.^{9,13} Edington and Bridges¹⁴ have provided evidence that, in the CNS, thrombosis and ischemia follow direct endothelial infection. However, CNS vasculitis and endothelial infection have been found in young foals with minimal neural lesions.⁸ Whether immune factors are also operative in the genesis of vascular injury is uncertain. Circulating immune complexes have been demonstrated and may involve antibodies to subtype 2 of EHV-1 virus.

Why this vasculopathy consistently affects blood vessels of the CNS (other organs may be affected) is unknown. It is of comparative interest that CNS vasculitis and ischemia may occur with human herpes varicella-zoster infection¹⁵ and occasionally with herpes simplex.

The EHV-1 has been incriminated as the cause of an epizootic of chorioretinitis, optic neuritis, and meningoencephalitis in alpacas and llamas¹⁶ and may be responsible for other cases.¹⁷

References are on page 182.

EQUINE INFECTIOUS ANEMIA

Equine infectious anemia (EIA) is a lentivirus infection of the horse. Clinical disease may follow an acute, subacute, or chronic course and is usually manifest as pyrexia, anemia, edema, weight loss, and hemorrhage. The lesions of EIA involve many organs. On rare occasions, horses present

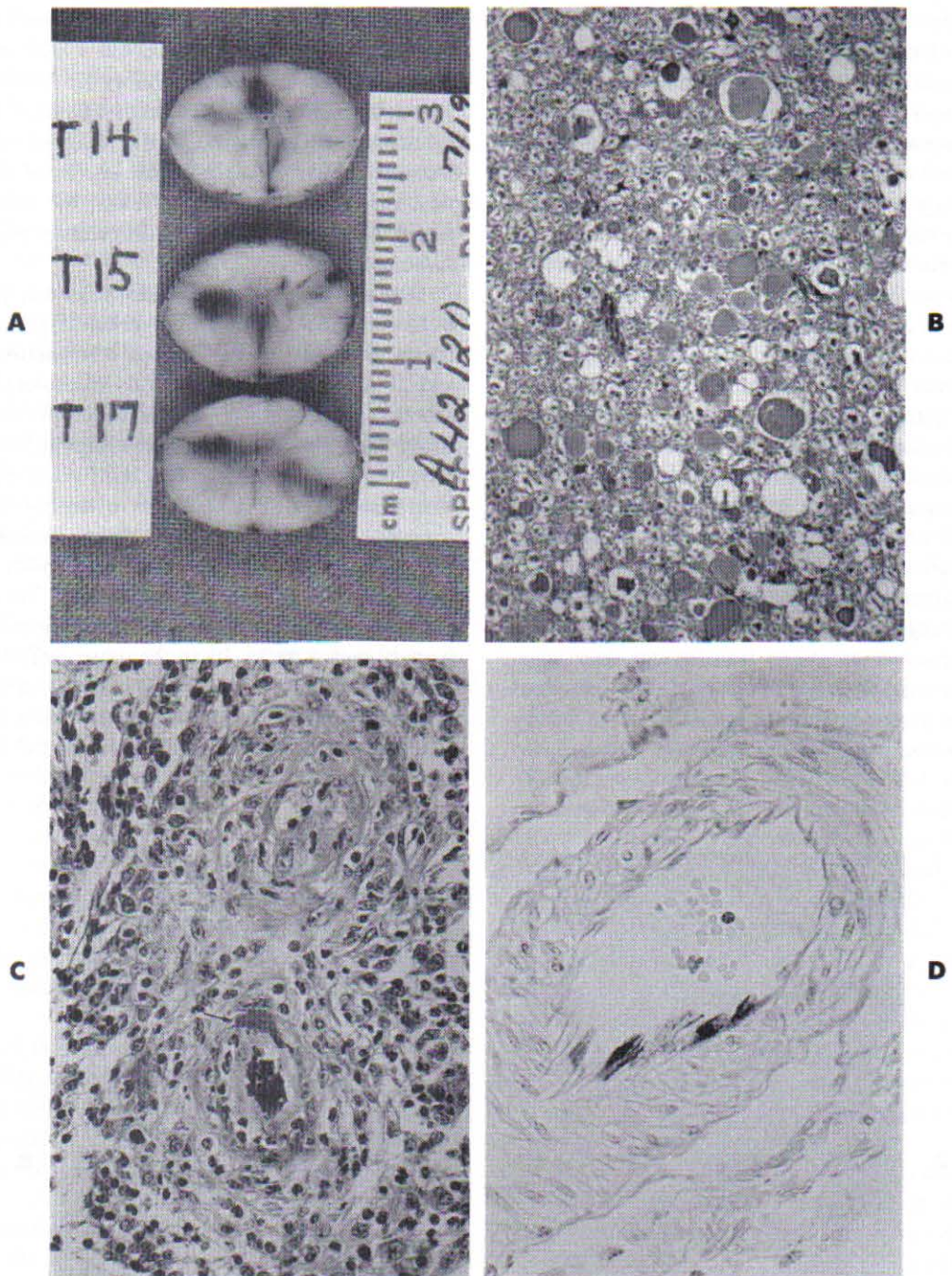


Fig. 3-38. Equine herpesvirus vasculitis and myelopathy. **A**, Hemorrhagic spinal cord necrosis along the course of radial blood vessels. **B**, Band of swollen axons and spongy myelin in spinal cord white matter. (H&E, $\times 140$.) **C**, Florid vasculitis with focal fibrinoid necrosis (*arrow*), cerebral leptomeninges. (H&E, $\times 350$.) **D**, Herpes viral antigen in endothelial cells in a noninflamed meningeal artery. (Immunocytochemistry, $\times 560$.)

purely with signs of neurological disease,¹ although the finding of neuropathological lesions in the absence of overt CNS dysfunction is more common.² The CNS signs are usually referable to spinal cord disease and include ataxia from symmetrical proprioceptive deficits in all limbs.

Examination of CSF is helpful; lymphoplasmacytic inflammatory changes in the neuraxis are reflected in elevations of protein and white blood cells.^{1,3} The CSF may be mildly xanthochromic. Gross examination of the surface of the fresh brain and spinal cord may reveal granularity and opacity, suggesting leptomeningeal inflammation. Microscopically this is confirmed, as is a diffuse granulomatous ependymitis and choroid plexitis. The inflammatory reaction is conspicuously surface related about the ventricular systems, central canal, and leptomeninges. The cell population consists of plasma cells, lymphocytes, and macrophages, with the occasional giant cell. Inflammation is most pronounced in the spinal cord. Involvement of the neuroparenchyma is secondary to perivascular extension or to disruption of ependymal cells, which results in necrosis of periventricular tissue. Positive serological evidence of infection (agar gel immunodiffusion test) may be obtained from the blood and CSF.

Infection of horses is persistent for life, and tissue injury, from which few organs escape, is immune-mediated. The pattern of CNS involvement shares features with visna, caprine arthritis encephalitis syndrome, and feline infectious peritonitis, other immunopathological diseases.

References are on page 183.

BORNA DISEASE

Borna disease is a viral encephalomyelitis that occurs in Germany and Switzerland. The spontaneous disease occurs primarily in horses and occasionally in sheep.^{1,2} Known as an encephalomyelitis of horses for more than 250 years,³ Borna has been studied since the 1920s, including demonstrations of its transmissibility to laboratory animals. However, many questions as to the nature of this neurotropic agent and the pathogenesis of the encephalomyelitis remain. Because behavioral disorders are characteristically observed in a variety of experimental hosts, the question has been raised whether Borna may be the cause of psychiatric illness in humans.⁴⁻⁶

In horses (and sheep), Borna disease has a low morbidity, but subclinical persistent infection is probably common. Many clinically normal horses have antibodies to Borna virus.⁷ The incubation period is prolonged (weeks or months).⁸ Once clinical disease develops, the course is typically brief and the mortality rate high, although a chronic, recurrent form is also recognized.³ Affected horses are at first anorectic and disinclined to move and have muscle tremors. There is a profound change in sensorium: Sometimes an initial phase of hyperexcitability gives way to depression, apathy, and somnolence.⁸ These deficits, together with paresis and ataxia, are progressive, leading to a moribund state in 10 to 22 days. Affected horses may have cortical blindness. Virus-specific antibodies can be detected in serum and CSF, and there is a pleocytosis.

Pathological changes are typical of the viral encephali-

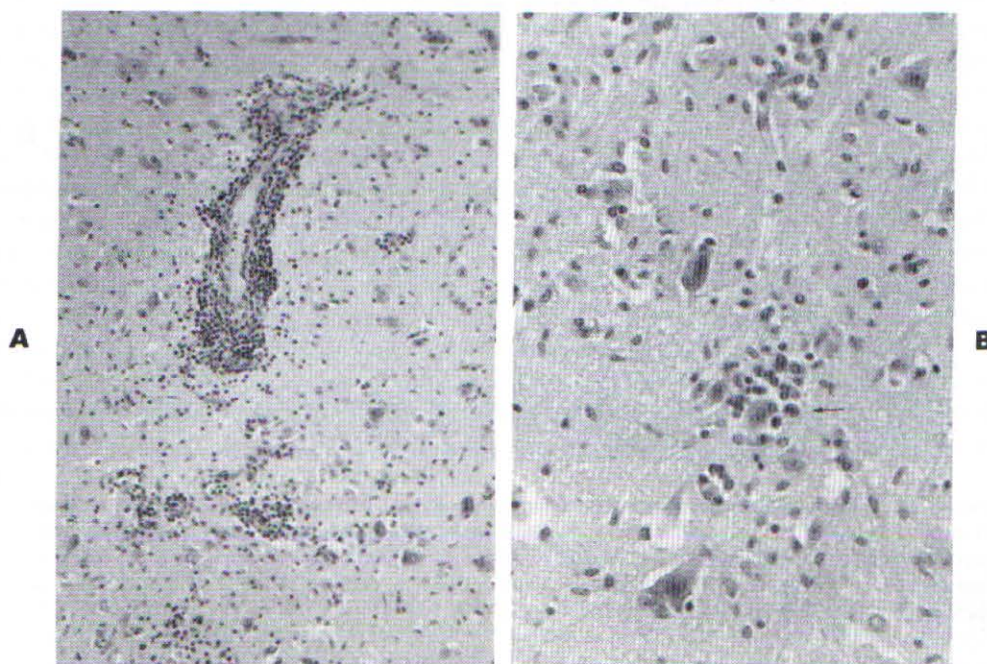


Fig. 3-39. Borna, horse. **A**, Lymphoplasmacytic cuffing and gliosis, cerebrum. (H&E, $\times 150$.) **B**, Microgliosis and neuronophagia (arrow), cerebrum. (H&E, $\times 350$.)

tides; the response is nonsuppurative, affects gray matter more than white, and can be found throughout the brain. Areas of predilection may relate to neurons with receptors for acetylcholine and other neurotransmitters.⁹ Affected areas are the lateroventral region of the cerebral cortex and the hippocampal gyrus, the hypothalamus, mesencephalon, and pons.¹⁰ Perivascular cuffs of lymphocytes and monocytes may be large, and these cells admix with proliferating microglia in the neuropil (Fig. 3-39). The meningeal surface is concurrently infiltrated by mononuclear cells. Degenerate neurons are of moderate numbers,¹¹ and some undergo neuronophagia. The diagnostic Joest-Degen inclusion bodies, which are acidophilic with a clear halo, are found within the nuclei and less frequently the cytoplasm of neurons, especially the larger neurons. Viral antigen is demonstrable in the nucleus, perikaryon, and processes¹⁰ and, in prolonged infections, in astrocytes.¹¹ Inflammation spills from the gray into subjacent white matter tracts and involves nerve roots and the spinal ganglia. Electron microscopic studies have demonstrated the disruption of the neuronal perikaryon but unequivocal viral structures have not been identified. Pathological changes in the brain of sheep with Borna disease are similar in nature and distribution to those in horses.

The **rabbit** is readily susceptible to Borna disease following inoculation with infectious brain tissue. Severe, acute meningoencephalitis and retinitis ensue; viral antigen is mainly demonstrable in neurons.¹² Intracerebral inoculation of brain tissue into **rats** produces a curious biphasic behavioral disorder: An early, frenzied hyperactive stage correlates with the development of the inflammatory response to virus in the CNS. This inflammation then subsides, despite viral persistence, and is marked clinically by an inactive, more passive state and the development of blindness.¹³ Immunosuppression of Borna-infected rats or the passive transfer of spleen cells implicate immune mechanisms in the production of CNS injury,¹⁴ in particular CD4 + T cells.¹⁵

The agent of Borna is an unclassified, enveloped RNA virus. It is readily adapted to tissue culture,¹⁶ where it grows in a highly cell-associated state producing a persistent, non-cytopathic infection. In vivo, viral spread is believed to occur within axons, a feature of other highly neurotropic agents.

Borna remains endemic in central Europe. It has been proposed that the agent of Near Eastern equine encephalomyelitis, a tick-borne viral encephalomyelitis of horses, cattle, and sheep, is identical to Borna.^{17,18} This remains to be established.

References are on page 183.

MURINE CORONAVIRUS ENCEPHALOMYELITIS

Murine coronavirus is an important cause of hepatitis in mice, especially in T cell-deficient (nude) mice. The JHM strain of murine coronavirus is a neurotropic variant, first

isolated and characterized in 1949.^{1,2} Although spontaneous episodes of CNS infection with this agent in mice do not seem to be common, the JHM isolate has become an important tool for the experimental study of virus-induced demyelinating encephalomyelitis. The clear advantages offered by murine models of demyelinating disease include the ability to define and manipulate the genetic background of the experimental host, the ability to dissect the effects of various components of the immune system upon disease development, and more recently the capacity to alter the virus genetically and to work with transgenic infections.

The JHM virus was first isolated from young mice with spontaneous flaccid paraplegia.¹ Virus was propagated by the intracerebral inoculation of brain suspension into similarly aged mice, and to this day the intracerebral route is commonly employed to induce disease.

Lesions in the neuraxis of mice involve gray matter and white matter to varying degrees. This dual pathology is a feature shared by other viral encephalitides such as canine distemper and Theiler's disease of mice. With the JHM coronavirus, gray matter lesions are necrotizing and are associated with a polymorphonuclear cell response.² They are common in the hippocampus and olfactory lobes. Meningitis accompanies the development of these cerebral lesions, and multinucleated syncytia, apparently derived from pial cells, endothelia, and large mononuclear cells, are a conspicuous feature. Spongy demyelinating lesions are prominent in the brain stem and spinal cord, accompanied at first by polymorphonuclear and later mononuclear leukocytes or sometimes occurring in the absence of inflammatory cells. Electron microscopic studies of the white matter reveal early myelin vesiculation and fragmentation and stripping of myelin sheaths from intact axons by macrophages.^{3,4}

Infection of young (4- to 6-week-old) mice induces encephalomyelitis with patchy demyelination in the brain stem and spinal cord. Some animals survive the acute infection and remyelinate;⁵ others develop a chronic demyelinating disease.⁶ The use of viral variants such as temperature-sensitive mutants, which are less neurovirulent, allows a chronic, persistent CNS infection to develop with recurring episodes of demyelination.^{7,8}

The JHM coronavirus is believed to cause demyelination by infecting oligodendrocytes, leading to their degeneration.³ Infection is not limited to these cells, however, but also involves neurons and other glial cells.⁴ Other investigators have provided evidence in support of immune mechanisms of demyelination in this infection.⁹

Cheever and colleagues demonstrated in 1949 that the JHM virus would induce encephalitis in **rats**. This murine coronavirus has been further studied in the rat, both in vivo¹⁰⁻¹² and in vitro.¹³ As a model of demyelinating disease, it offers the advantage of more pronounced white matter than gray matter involvement.

References are on page 183.

MISCELLANEOUS CNS INFECTIONS

Many infectious agents, although primarily affecting tissues of the respiratory, gastrointestinal, or other systems, occasionally wander into the CNS. For some microbes the incursion is mild, perhaps to be revealed unexpectedly at postmortem examination. A few agents incite persistent infections, and CNS involvement may be demonstrable in the absence of neurological disease; one such example is the bovine viral diarrhea virus in adult cattle (Fig. 3-40).^{1,2} With other pathogens, neuraxial involvement may be sufficient to incite signs of neurological disorder with some regularity. In this section we shall discuss this miscellaneous group of pathogens.

Several rickettsioses of animals, to a lesser or greater degree, involve the CNS. In cattle, sheep, and goats, rickettsial diseases are often generically designated as tick-borne fever;³ many are relatively benign. In Scotland, there is some suspicion that staphylococcal pyemia and louping ill encephalomyelitis are favored in lambs with tick-borne fever. Similar interactions, predisposing to encephalomyelitis, may occur elsewhere.

In Africa, **heartwater** is a tick-borne rickettsial disease of cattle, sheep, and goats caused by *Cowdria ruminantium*. The organism is transmitted by *Amblyomma* ticks and is found in the host's blood, lymphoreticular tissues, and vascular endothelia. Heartwater is so named for the feature of hydropericardium, but clinically a neurological disorder is common, with nervous chewing movements, frothing,

twitching of the eyes, muscle trembling, circling, forelimb hypermetria, and terminally seizures. Cerebral vasculitis is the basis for these signs, with parasitism of endothelial cells, hemorrhage, and local ischemia.⁴ Rickettsial organisms can be demonstrated in fixed brain smears stained with Giemsa.⁵

Rocky Mountain spotted fever (RMSF) is caused by *Rickettsia rickettsii* and in the United States occurs in the environment of its vector ticks, *Dermacentor andersoni*, *D.*

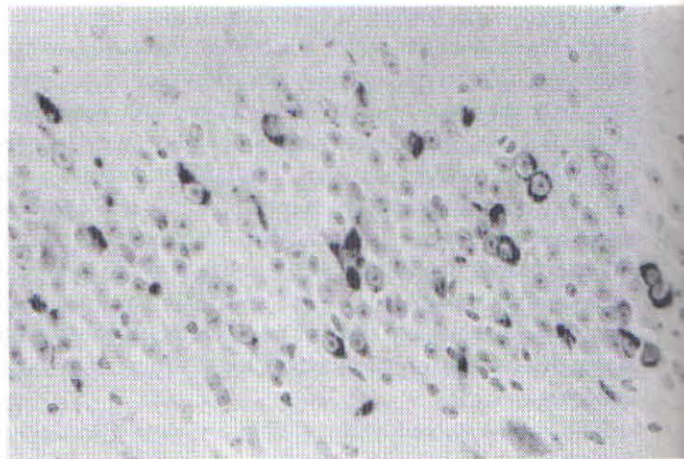


Fig. 3-40. Bovine virus diarrhea antigen in the granule cells of the hippocampus, cow. (Immunocytochemistry, $\times 350$.)

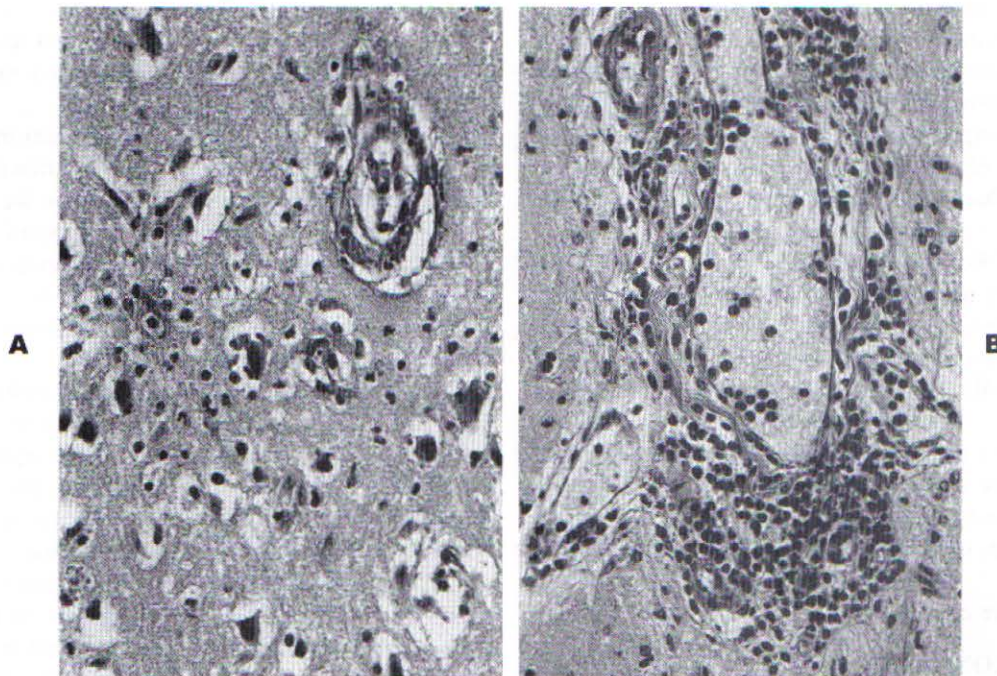


Fig. 3-41. A, Rocky Mountain spotted fever, dog. Fibrinoid degeneration of a small vessel and tissue neutrophilia, cerebrum. (H&E, $\times 350$.) B, European tick-borne encephalitis, dog. Nonsuppurative meningitis, cerebrum. (H&E, $\times 350$.)

variabilis, and *Amblyomma americanum*.⁶ It is reported in North, Central, and South America,⁷ and related spotted fever rickettsiae cause similar illnesses in various parts of the world. Serological evidence indicates that a range of domestic animals may become infected, but clinically the disease is important in the **dog**. The initial presenting signs are non-specific: high fever, depression, lethargy, and vomiting.⁸ Petechial to ecchymotic hemorrhages are found on the mucosae but less often on the skin than occurs in humans. Neurological abnormalities include an altered sensorium, nystagmus, ataxia, and circling^{6,8} and suggest the likelihood of global brain injury. The pathology of RMSF is fundamentally a vasculitis (Fig. 3-41) that affects arterioles, capillaries, and venules⁹ in many organs, particularly the meninges, retina, and skeletal muscle.¹⁰ Extension of the inflammatory reaction in the CNS produces a meningitis and multifocal encephalitis. The walls of affected blood vessels are infiltrated with neutrophils and mononuclear cells,¹¹ and neutrophils migrate into small areas of necrosis in the parenchyma. The diagnosis is substantiated by the demonstration of rising serum titers or by immunofluorescent procedures.⁷

Canine ehrlichiosis is caused by *Ehrlichia canis* and transmitted by the brown dog tick *Rhipicephalus sanguineus*. The disease is recognized in several American states and came to prominence in military dogs working in Vietnam.¹² Clinically, this rickettsiosis shares several features with Rocky Mountain spotted fever in dogs.⁷ Initially there is anorexia, weight loss, fever, and lymphadenopathy. Mucous membranes are pale, and there is anemia, thrombocytopenia, and sometimes leukopenia. The clinical course is prolonged and variable, probably depending on the strain of the organism and the presence or absence of intercurrent disease. Some dogs show a tendency to bleed, with epistaxis and melena. Neurological disease is seen in perhaps a third of affected dogs.⁷ In a study of 100 dogs that died of canine ehrlichiosis in Southeast Asia, limb edema and disseminated hemorrhages were found in many organs.¹³ Microscopically, CNS lesions were found in 96% of the group, mainly a meningitis of mononuclear cell type, particularly with plasma cells, which were often disposed about venules. In a small proportion of cases, a nonsuppurative meningoencephalitis was observed. *Ehrlichia morulae* may be found within mononuclear cells from the CSF.¹⁴

Neorickettsia helminthoeca is the cause of **salmon poisoning**, a lethal disease of **dogs** and **foxes** on the Pacific West Coast. The infection is acquired by eating salmon, trout, or other fish that harbor metacercariae of the fluke *Nanophyetus salminicola*. The flukes, which require two intermediate hosts (first snails and then fish), act as reservoirs of the rickettsial agent. Clinical signs of the disease are non-specific and include severe depression, fever, paresis, oculonasal discharge, and diarrhea. Postmortem findings are of marked hypertrophy of lymphoid tissues with lymphocytic depletion and reticulum cell hyperplasia. CNS

involvement is common¹⁵ but usually clinically silent. There is a diffuse leptomeningitis that may be evident at necropsy as meningeal opacity or cloudiness. The cellular population is mainly mononuclear: histiocytes, lymphocytes, and plasma cells. These changes are most severe in the cerebellum. In some cases, such mononuclear cells form perivascular cuffs and infiltrate the adventitia of arterioles and venules of the brain. Adventitial cell hyperplasia may be evident. Small foci of reactive glial cells, admixed with hematogenous types, are also found in the neuroparenchyma. Elementary bodies can be demonstrated in histiocytes of the lymphoid organs and in the leptomeninges.

Bacterial infections of the nervous system are mostly associated with suppurative leptomeningitis and with brain or spinal cord abscesses and are discussed elsewhere. Septicemic **salmonellosis** in pigs may be manifest as a vague neurological syndrome, a consequence of a disseminated pyogranulomatous meningoencephalomyelitis with vasculitis.^{16,17} **Tuberculosis** of the CNS has largely disappeared with the eradication of *Mycobacterium bovis* from cattle populations. Hartley¹⁸ recorded a focal necrotizing encephalitis and vasculitis in cattle with visceral tuberculosis, possibly reflecting a hypersensitivity reaction to the systemic infection. In equine **glanders**, hematogenous dissemination of the *Pseudomonas mallei* bacillus may produce hemorrhagic foci of infection in the brain. **Tyzzers' disease** (*Bacillus piliformis* infection) with hepatitis, enteritis, and suppurative encephalitis has been recorded in gerbils.¹⁹

Sporadically, many **fungal agents** have been noted to cause encephalomyelitis (Figs. 3-42 and 3-43), including *Aspergillus* spp.,^{20,21} *Mucor* spp.,²² and *Candida* spp. An underlying predisposing factor should be sought, which may include primary or acquired immunosuppressive conditions, the prolonged administration of antibiotics, or some chronic debilitating illness (diabetes mellitus, neoplasia). Disseminated *Aspergillus terreus* infection, with neural involvement, has been observed in German Shepherd dogs in Australia²³ and the United States,^{20,24} and one of us (BAS) studied a fungal encephalitis, possibly aspergillosis, in a German Shepherd dog in England.

Cryptococcus neoformans is a common saprophytic yeast with a worldwide distribution that is an occasional pathogen in animals and humans, more commonly in warm, humid climates. Its sources in nature are numerous, including the soil, grass, and milk;²⁵ one in particular is the droppings of pigeons. In humans, up to 85% of cryptococcosis is associated with an underlying debilitating disease²⁶ such as tuberculosis, leukemia and lymphoma, diabetes mellitus, drug-induced immunosuppression, and, more recently, AIDS.²⁷ In contrast, the necessity for predisposing factors is less clear in animals; although some animals with cryptococcosis are debilitated, this generally appears to be a consequence of the infection.

Cryptococcosis is most common in **cats** and **dogs**; it occurs occasionally in horses and only rarely in other spe-

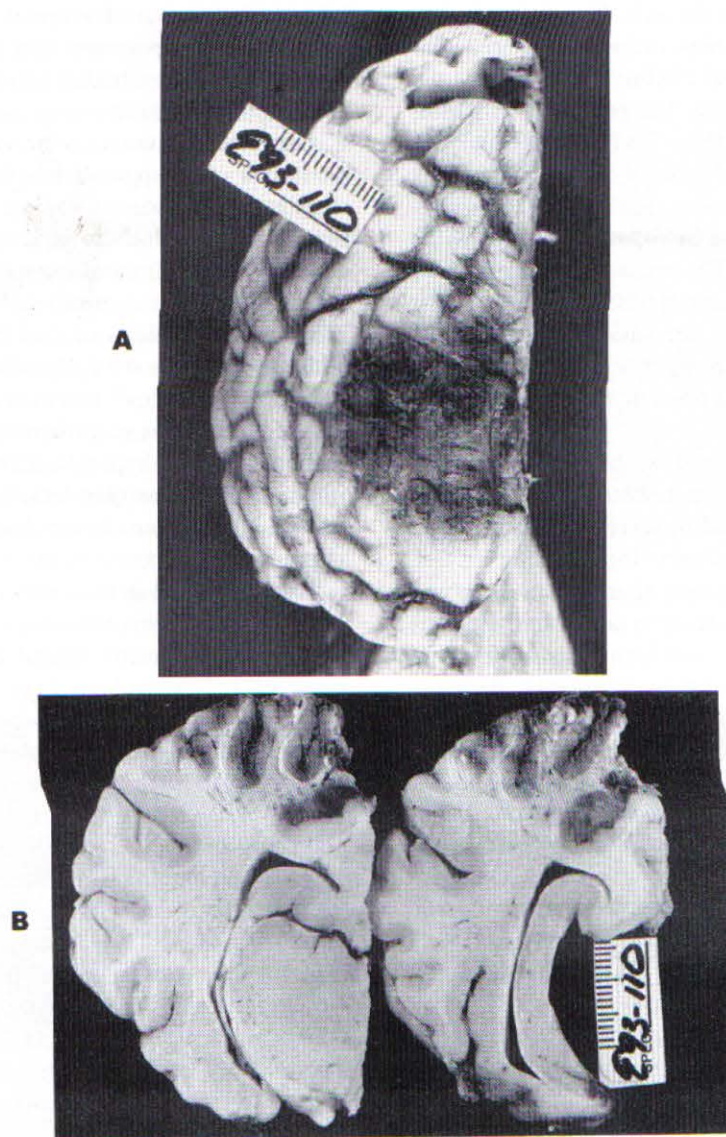


Fig. 3-42. Mycotic encephalitis (mucormycosis), steer. **A**, Area of cerebral discoloration and necrosis. **B**, Transverse sections reveal prominent meningeal vasculature (thrombosis) and necrosis of the cerebral cortex and underlying white matter.

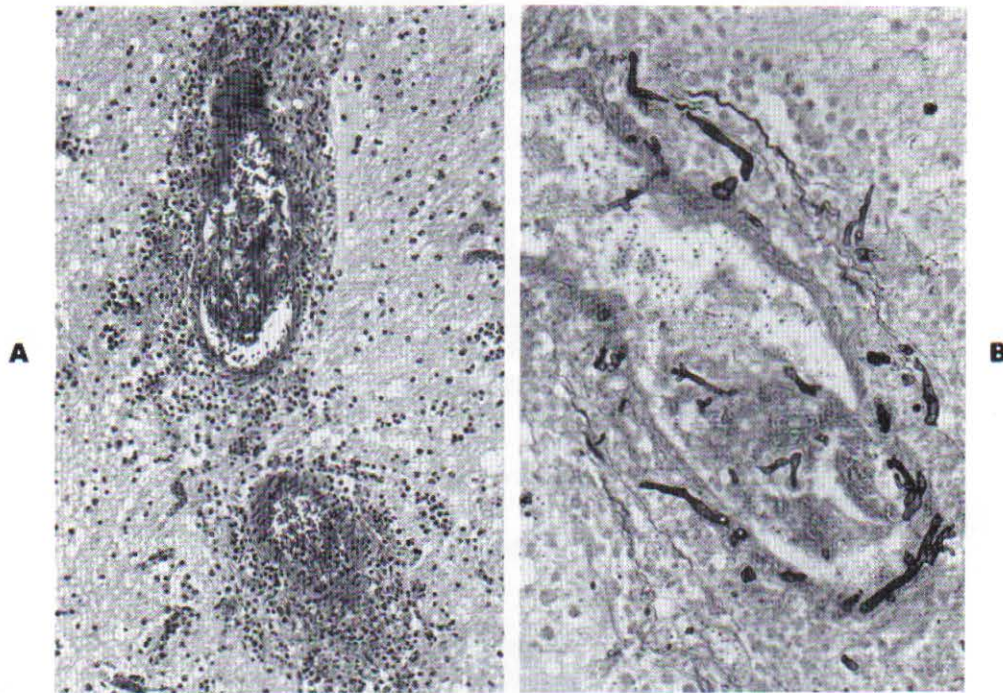


Fig. 3-43. Mycotic encephalitis (aspergillosis), calf. **A**, Intense vasculitis, cerebrum. (H&E, $\times 180$.) **B**, Fungal hyphae in vessel wall and lumen. (Grocott, $\times 360$.)

cies. In cats and dogs, the clinical presentation may reflect skin disease, upper respiratory tract disease, CNS disease, skeletal disease, or combinations of these.^{25,28} Although therapy is available, infection is often generalized, and affected animals are often euthanized. Meningeal involvement is common, reflecting one site of predilection. In some, the lesion extends to the ependymal surface of the ventricular system and adjacent parenchyma. Grossly, the leptomeninges vary from unremarkable to cloudy and thickened, perhaps associated with a gelatinous, mucoid exudation (Fig. 3-44). Section of the brain may reveal small cystic spaces, up to a couple of millimeters in diameter, within the parenchyma. The sulci of the cerebrum may be greatly widened. In cats, microscopic findings are of numerous confluent organisms filling the subarachnoid space and expanding the sulci; tightly packed yeast bodies may impart a soap bubble appearance. Cystic spaces within the neuroparenchyma are actually greatly expanded perivascular spaces (Fig. 3-45, A), and a blood vessel within the "cysts" can often be identified. In H&E-stained sections, the organism has a round to ovoid cell body and a clear capsule seen as a halo that stains strongly with PAS or mucicarmine. The encapsulated organism measures up to 20 micrometers, and budding forms may be seen. In cats these organisms generally provoke only a mild (nonsuppurative) inflammatory response, within either the meninges or neuroparenchyma. In contrast, canine lesions are much more cellular; the response is more granulomatous (Fig. 3-45, B),²⁸

with epithelioid macrophages (some containing the yeast), lymphocytes, and plasma cells in the brain and meninges. Ocular involvement sometimes accompanies CNS invasion, and the organism is found between the choroid and retina. Cryptococcosis of the CNS can frequently be diagnosed by examination of CSF. Identification of the organism is facilitated by staining with India ink. Attempts to culture the organism from CSF and exudates are frequently rewarding. Transmission to mice can also be employed to confirm the diagnosis. Within paraffin-embedded tissue, the agent can be identified by immunofluorescent procedures.²⁹ A latex agglutination test, which measures cryptococcal polysaccharide capsular antigen in serum or CSF, is employed in humans and has been used in the cat^{30,31} and horse.³²

Cryptococcus neoformans infection has been reported in the meninges of horses³²⁻³⁴ and rarely in other species.³⁵

The epidemiology and pathogenesis of cryptococcosis are uncertain. Infection is probably acquired from the environment rather than other animals. Primary infection may occur in the upper respiratory tract, sinuses, or oropharynx, with secondary spread to the CNS and other organs. The ability of *Cryptococcus* to persist in the CNS may be related to its facility for utilizing catecholamines, thus circumventing the harmful effects of catecholamine oxidation.³⁶

Several groups of fungi acquire regional importance in environments that facilitate their survival, for example, the southwestern parts of the United States. In patients often known or suspected of having underlying predisposing dis-

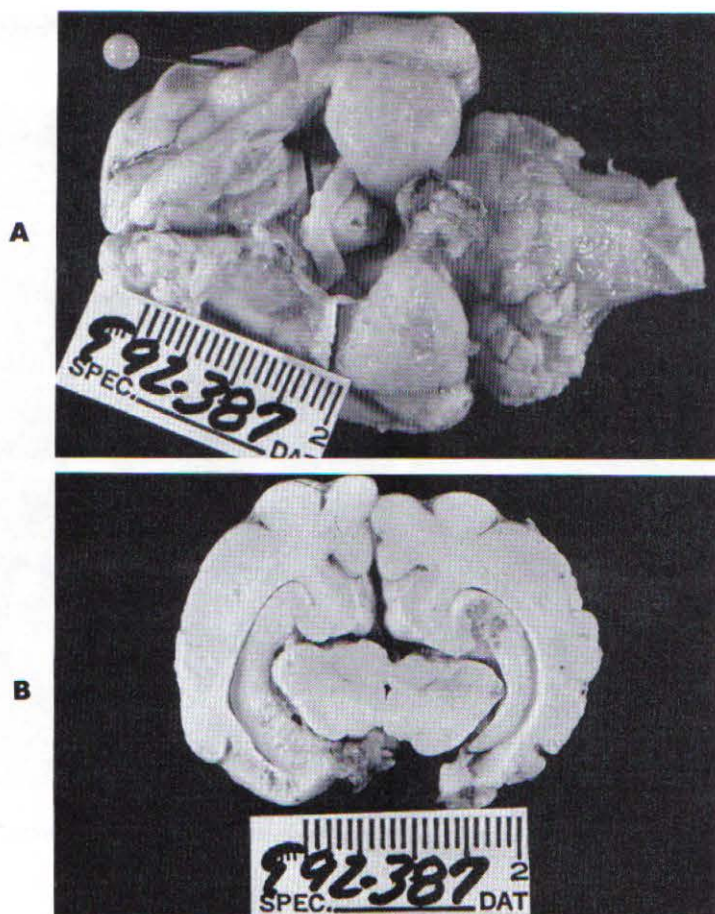


Fig. 3-44. Cryptococcosis, cat. **A**, Basal meninges appear thickened and mucoid. **B**, Soap bubble appearance within the parenchyma.

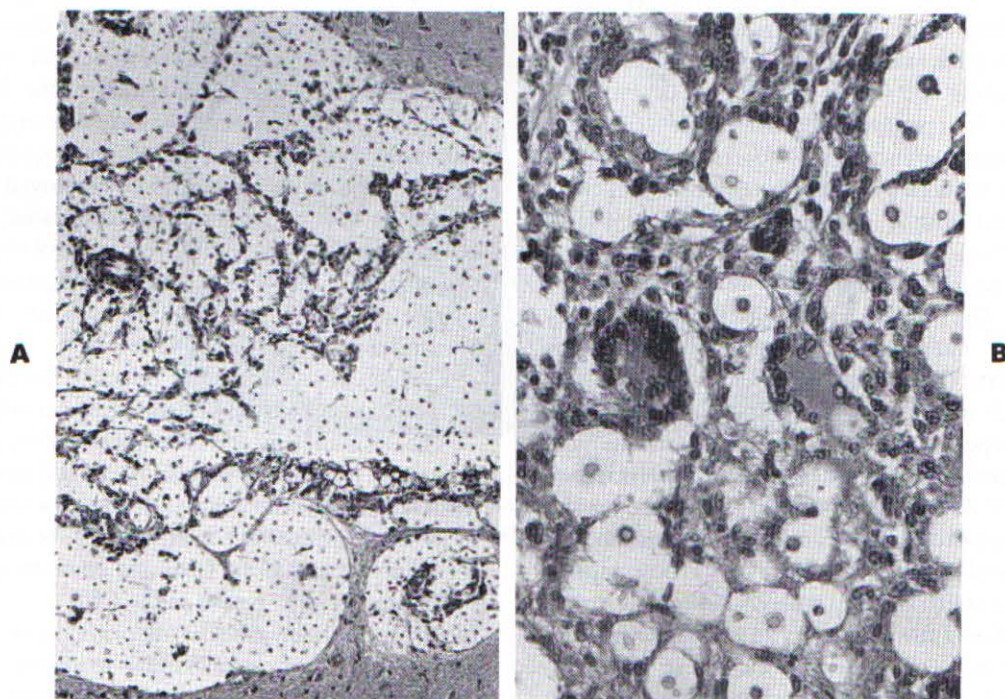


Fig. 3-45. Cryptococcosis. **A**, Multiple cavities formed by expanded perivascular spaces filled with cryptococcal organisms, hippocampus, cat. (H&E, $\times 140$.) **B**, Cryptococcosis, dog, with giant cell response. Some organisms are budding. (H&E, $\times 350$.)

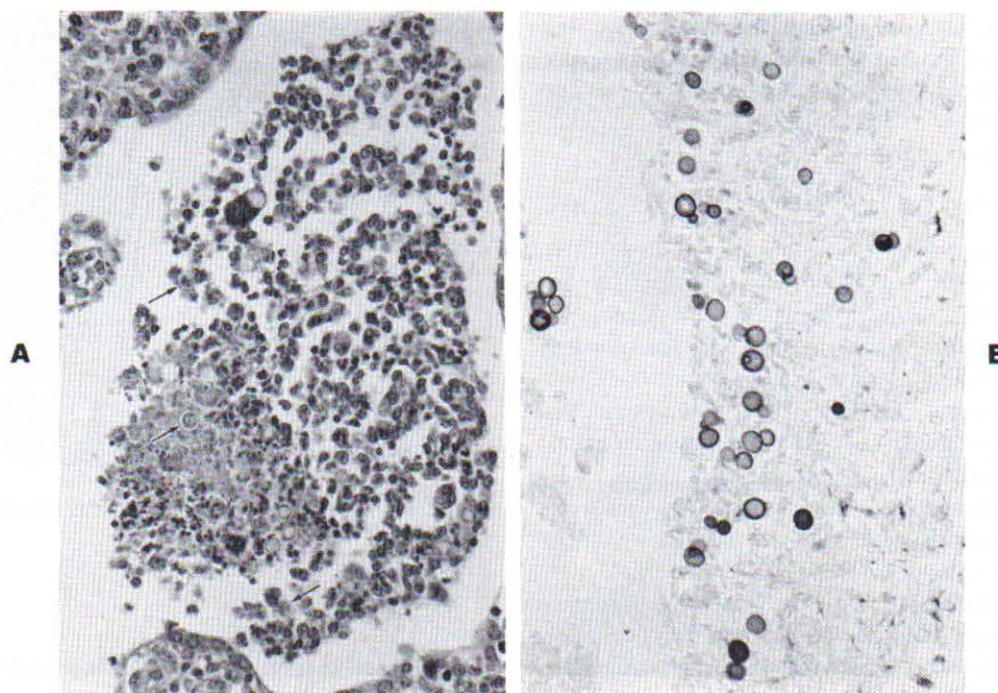


Fig. 3-46. Blastomycosis, dog. **A**, Pyogranulomatous inflammation in choroid plexus. Note organisms (arrows). (H&E, $\times 350$.) **B**, Yeast bodies at ependymal surface. (GMS, $\times 350$.)

orders, organ involvement may be multiple following the establishment of a primary infection in the skin, respiratory tract, gastrointestinal tract, or elsewhere. A CNS involvement is probably more common than the sporadic reports would suggest. At necropsy, granulomatous lesions are commonly found in many organs, and, regardless of the agent, they have a common form. The center may be necrotic or contain a pool of neutrophils around which epithelioid macrophages and multinucleated giant cells are clustered, and these merge into a zone of lymphoid cells. The fungal agent is found as free hyphae or in yeast form, the latter often within macrophages.

Blastomycosis is caused by *Blastomyces dermatitidis*,³⁷ and pyogranulomatous encephalitis (Fig. 3-46) has been described in the dog^{38,39} and the cat.⁴⁰ The diagnosis is made by identifying the budding organisms in the lesions, by culture, and by agar-gel immunodiffusion tests. Disseminated *Histoplasma capsulatum* infection in the dog is well recognized,⁴¹ but neurological disorder in **histoplasmosis** is uncommon. In one case,⁴² paresis and ataxia progressing to tetraparesis and cranial nerve deficits followed a primary gastrointestinal tract disorder. The CSF was examined and supported a diagnosis of CNS inflammatory disease. Reports of *Coccidioides immitis* infections that involve the CNS are sparse,⁴³ whereas granulomatous disease involving multiple visceral organs is common in the hot, dry zones of North, Central, and South America where **coccidioidomycosis** is endemic. A few episodes of CNS mycosis caused by op-

portunistic, pigmented (dematiaceous) fungi have been recorded in the dog and cat.^{44,45} In these **phaeohyphomycoses**, brown branching hyphae are observed within the areas of pyogranulomatous inflammation. *Cladosporium bantianum* (trichoides) is the most important agent.⁴⁴ As for other mycotic encephalitides, intravascular growth and thrombosis may be observed.

An association between **spirochetal infection** and neurological disease has long been known. Of historical and, sadly, continued importance is *Treponema pallidum*, the cause of syphilis. Occasionally, leptospira infection produces a meningitis. Of both human and veterinary importance is *Borrelia burgdorferi* infection (Lyme disease), which is transmitted by ixodid ticks. In humans this is a chronic relapsing infection with initial skin lesions and muscle and joint pain. Weeks to months later, cardiac and various neurological manifestations may be seen, including meningitis, polyneuritis of cranial nerves, and radiculoneuritis.^{46,47} A further tertiary manifestation is arthritis. There is serological evidence of transmission of this spirochete to domestic and nondomestic animals,^{48,49} and an association between borreliosis and arthritis has been established in animals.^{49,50} Reports of neurological disease in animals with borreliosis are rare,^{51,52} and the role of this spirochete in CNS and/or PNS disease in animals is yet to be established. Named for the county in Connecticut in which it was epidemic, Lyme disease has been recognized in Europe since the early part of this century and occurs in many countries.

Prototheca are saprophytic algae that may cause cutaneous, ocular, and gastrointestinal infections in animals. Disseminated protothecosis with central nervous system involvement has been recorded in the dog.⁵³⁻⁵⁵

References are on page 183.

MENINGITIS AND BRAIN ABSCESES

In meningoencephalitis (or meningoencephalomyelitis), the brunt of the injury is borne by the neuroparenchyma, and meningeal inflammation is often patchy. In this section, we are mostly concerned with the bacteria that primarily induce inflammation of the leptomeninges and, often concurrently, other serous membranes. It is worth noting that examples of pure meningitis of viral cause, so-called aseptic meningitis in humans, are not recognized in animals. By definition, **leptomeningitis** is inflammation of the pia mater and the arachnoid, whereas **pachymeningitis** is inflammation of the dura mater.

Bacterial meningitis is rare in dogs and cats, in marked contrast to its high incidence in newborn farm animals. Sporadic cases have been recorded in mature animals,^{1,2} sometimes caused by anaerobes.³ Most instances of canine leptomeningitis are sterile, responsive to corticosteroids, and thought to be immune-mediated (see the section on canine meningeal polyarteritis). Meric⁴ has reviewed the causes of meningitis in the dog; a subsequent report described a subclinical granulomatous leptomeningitis in dogs with *Escherichia coli* antigens.^{4a}

Bacterial leptomeningitis occurs endemically in neonatal farm stock (particularly calves, lambs, and piglets) and is associated with coliforms, streptococci, pasteurellae, and mycoplasma. Other bacteria incite similar changes but do so in certain species only: in pigs, *Haemophilus suis* in Glasser's disease and *Salmonella dublin*;⁵ in foals, *S. typhimurium* and *Actinobacillus equuli*; and *H. agni* in lambs are some examples. Clinically these syndromes are marked by pyrexia, anorexia, and drowsiness or depression in the early bacteremic phase of the infection. Neurological signs are diffuse and nonspecific. They often reflect cerebello-medullary involvement: paresis, ataxia, balance deficit, abnormal nystagmus, and head tremor. When terminal, prostration, opisthotonus, semicoma, and occasionally seizures will be seen. The CSF is cloudy, may contain flakes of fibrin, and will show a pleocytosis (largely polymorphonuclear), elevated protein, and lowered glucose. A Gram stain of CSF sediment after centrifugation is useful. Cultures are usually definitive if antibiotics have not been employed.

At necropsy, there are typically varying combinations of purulent or fibrinopurulent peritonitis, pleuritis, pericarditis, endophthalmitis, polyarthritis, and leptomeningitis. The brain is swollen, soft, and moist; it may be herniated, resulting in coning of the cerebellar vermis and displacement of the parahippocampal gyri under the tentorium cerebelli. The latter gyri compress the brain stem, indenting its dorsolateral surface. The leptomeninges are cloudy and grayish, particularly over the sulci, where most exudate accumulates.

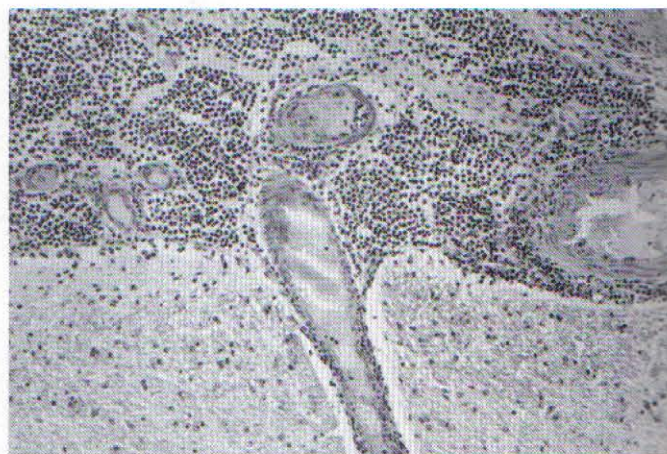


Fig. 3-47. Suppurative leptomeningitis, medulla, calf. (H&E, $\times 140$.)

This serocellular effusion gravitates ventrally, fills the basal cisterns, and so is particularly conspicuous over the ventral surface of the brain stem; it may continue caudally along the spinal cord. Transverse sections of the brain may reveal prominent and thickened choroid plexuses and a roughened, granular quality to the ventricular surfaces, indicating the presence of ependymitis. Occasionally exudate is found in the ventricles. If the exudate plugs the aqueduct, hydrocephalus will occur in the lateral and third ventricles.

Microscopically, an abundant effusion of polymorphonuclear cells, a few mononuclear cells, and a variable quantity of fibrin distend the subarachnoid spaces (Fig. 3-47). Meningeal blood vessels are dilated and congested, and neutrophils pave the endothelium and percolate through the vessel wall; some vessels are thrombosed. Some inflammation and edema of the dura are to be anticipated also. The accumulation of inflammatory cells in the meninges can be accentuated at points of CSF drainage, such as the arachnoid villi and nerve sheaths.⁶ The exudate in the subarachnoid space may extend along blood vessels into the adjacent parenchyma but shows little tendency to breach the pial membrane to involve the subjacent brain or spinal cord. In contrast, the ependymal surface offers much less resistance such that a ventriculitis will also involve the immediate subependymal zone of the brain. Inflammatory cells are also found in the stroma of the choroid plexuses, and exudate may be observed overlying focal erosions of plexus epithelium. Small focal areas of necrosis, often associated with vascular thrombosis, may be found scattered through the brain.^{7,8}

The leptomeninges are prone to invasion by a variety of commonly encountered environmental bacteria in the first month of life. Disseminated infection, including the CNS, may result from the failure of transfer of colostral antibodies.⁹ In somewhat older animals, septicemic disease with meningitis is associated with a somewhat different spectrum

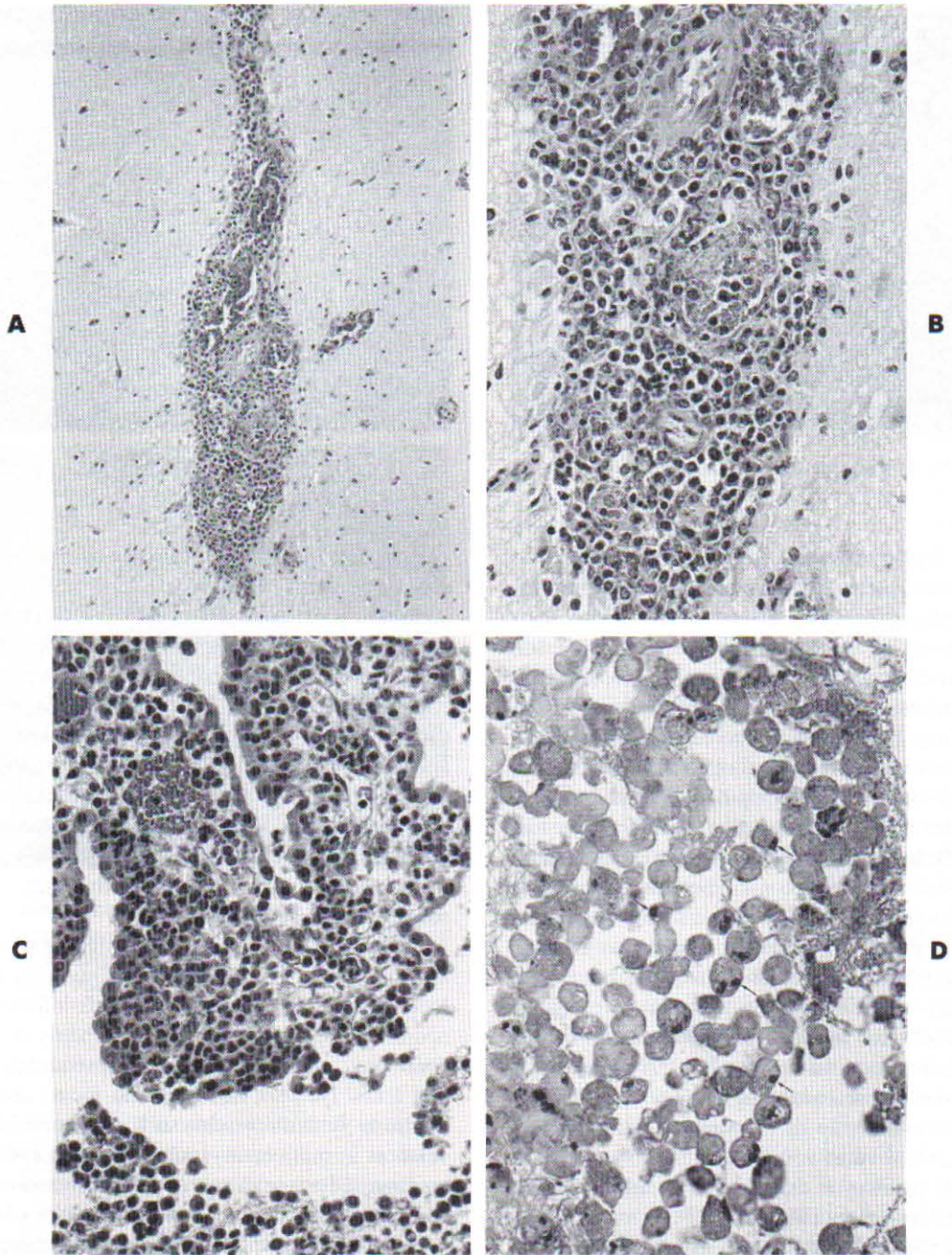


Fig. 3-48. Streptococcal meningitis, pig. **A**, Meningitis in cerebral sulcus. (H&E, $\times 140$.) **B**, Detail from **A**. ($\times 350$.) **C**, Choroid plexitis. (H&E, $\times 560$.) **D**, Immunocytochemical demonstration of *S. suis* type II organisms (arrows) within monocytes. ($\times 875$.)

of bacteria that have the property of being primary pathogens, such as *Salmonella typhimurium* in foals and others previously mentioned. *Streptococcus suis* type II (unlike type I) is associated with leptomeningitis in older, post-weaned pigs¹⁰ (Fig. 3-48). The course in swine is often subacute and may be associated with cerebellar cortical necrosis with depletion of Purkinje and granule cell neurons.¹¹ These changes are presumably focal areas of infarction,

secondary to meningitis with vascular necrosis and the effects of brain swelling. At any age, trauma resulting in fracture may directly contaminate the meninges, brain, and spinal cord. In those forms of meningitis caused by gram-negative bacteria, lipopolysaccharide endotoxin probably contributes to lesion development¹² by inducing the release of inflammatory mediators such as tumor necrosis factor and interleukin-1.¹³



Fig. 3-49. Organized pituitary abscess, cow.

Microscopic leptomeningitis may be found in cases of infectious abortions, such as that caused by *Brucella abortus* in cattle¹⁴ and other abortigenic agents.¹⁵

Abscesses involving the CNS may be primarily extramedullary or intramedullary. Localized, extramedullary areas of suppuration are usually extradural and are often an extension from a primary focus in the calvaria (sinuses) or the vertebrae. In white-tailed deer, cerebral abscesses are much more common in the male population¹⁶ and appear to result from antler injury from sparring during the mating season. Similarly in male sheep, head butting can produce basisphenoid fractures that become infected. Suppurative arthritis or osteomyelitis of the vertebrae is a common cause of paraparesis in pigs,¹⁷ the infection sometimes initiated by tail biting. Vertebral body abscesses in lambs may extend into the epidural space, producing spinal cord compression.¹⁸ Epidural infection in the cat can follow a tail fracture or a purulent dermatitis involving the tail.^{19,20} Infections in the nasal chamber or paranasal sinuses may spread to intracranial structures by way of the venous circulation, as the valveless cerebral veins communicate with soft tissues of the head. This pathway is thought to explain the genesis of some pituitary abscesses (Fig. 3-49).²¹

Extension of the infection through the dura is unusual, and so more or less localization and encapsulation ensue. The clinical importance of these abscesses is related to their mass effect; they compress and displace the neural tissue, which is confined within the cranial cavity or vertebrae. In the brain, disruption of the vasculature in the compressed tissue produces (vasogenic) edema that spreads widely, particularly through white matter. Increased intracranial pressure (from both the epidural abscess and brain swelling) increases cerebral perfusion, which exacerbates the edema, thus creating a vicious cycle of events.

Abscesses in the parenchyma (Fig. 3-50) are often hematogenous in origin, multiple²² but sometimes single,²³ and like tumors in the cerebrum, tend to occur at the gray-white



Fig. 3-50. Brain abscess, sheep, cerebrum.

matter junctions. CNS embolization may occur during an acute septicemic infection (e.g., *A. equuli* in foals) or from a chronic point source such as a valvular endocarditis. In horses, disseminated forms of *Streptococcus equi* infection (strangles) will produce abscesses in several organs, including the brain.^{24,25} Suppurative otitis media/interna is commonly encountered in both small and large domestic animals. Extension of the infection to produce pontine and cerebellomedullary abscesses is seen in the pig (Fig. 3-51)²⁶ and sporadically in the cat. *Pasteurella multocida*, *Actinomyces pyogenes*, and *Corynebacterium pseudotuberculosis* are often isolated from such cases. Sometimes the source cannot be established.²³

Grossly, the abscess contents may be white or yellowish and fluid or semisolid. Bacterial invasion at first triggers local hyperemia, edema, neutrophil infiltration, and focal necrosis. Organisms are found in chains or small colonies, commonly within leukocytes. Subsequently, macrophages and a few lymphocytes enter the focus, and a reactive astrogliosis is demonstrable at the margins. Fibrous encapsulation is rudimentary unless the abscess is close to the meningeal surface, a source of collagenous tissue. Chronic meningeal fibrosis may impede drainage of CSF.²⁷

Either diffuse leptomeningitis or discrete cerebral abscess formation may follow bacterial invasion from a focus in a neighboring structure or from the bloodstream. The factors that dictate whether the ensuing CNS inflammation will be disseminated or localized are uncertain, although common experience shows that the neonate is prone to the dispersed pattern. In newborn farm animals delivered into the contaminated environment of the farmyard, bacteremic infection is not surprising. The newborn are immunologically naive, more so if they fail to receive protective immunoglobulins in the early (colostral) milk.²⁸ Portals of entry for bacteria are probably multiple, including the umbilicus, pharynx, and gastrointestinal tract. Cordy⁷ proposes that the concurrent occurrence of serositis, synovitis, and menin-

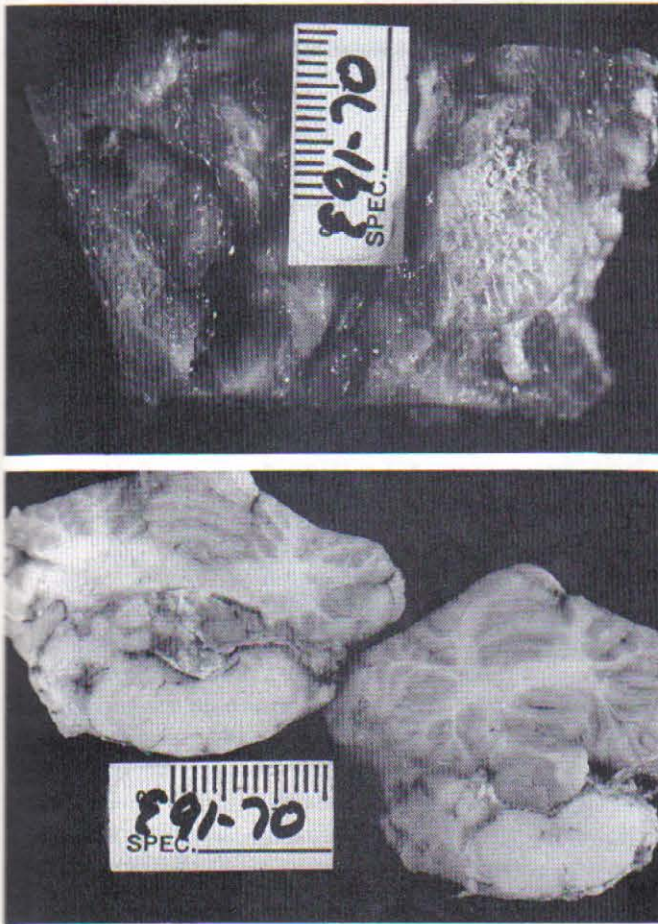


Fig. 3-51. Otitis media/interna with extension into CNS, pig. A, Otitis media. Tympanic bullae have been opened; the bulla on the left is destroyed by suppurative inflammation. B, Meningitis and cerebellomedullary abscesses.

goventriculitis in young calves, lambs, goats, foals, and piglets may be explained by the normal trafficking of monocytes to replenish resident surface macrophages in these tissues. In infections of neonates, monocytes with low bacteriocidal capacity may inadvertently carry bacteria to these tissues, triggering surface-related infections. The studies by Williams and Blakemore^{29,30} of experimental *Streptococcus suis* type II meningitis in pigs provide considerable credence to this hypothesis.

References are on page 184.

PARASITIC ENCEPHALOMYELITIS

In this section we shall review the helminths, cestodes, and trematodes that, sporadically or with some frequency, migrate through and inhabit the CNS. Protozoan agents are discussed elsewhere in this volume.

Verminous encephalomyelitis may result under two circumstances. The first is from the aberrant wanderings of a parasite that normally resides in that host; examples include

cerebral *Dirofilaria immitis* infestation in the cat¹ and *Strongylus vulgaris* migration in the brain of a horse. Second and much more common is the infestation of an aberrant host, such as when the meningeal worm of white-tailed deer infects goats, sheep, and other grazing animals. Under these circumstances, CNS involvement is exceptionally common, usually with more dire consequences than for the definitive host. Thus parasitic encephalomyelitis is encountered worldwide as a sporadic event in the first circumstance and regionally, as diseases of considerable importance, in the second. Sometimes the aberrant host is human.

In ruminants, several parasites are important. In North America, white-tailed deer (*Odocoileus virginianus*) spread larvae of *Parelaphostrongylus tenuis* in their feces. The larvae enter terrestrial mollusks (slugs or snails), which may be accidentally ingested by animals at pasture. Once freed in the intestine, larvae penetrate the wall of the gut and migrate across the peritoneal cavity to the spinal cord; spinal nerves may provide a convenient avenue into the CNS. Neurological disease caused by *P. tenuis* migration in the spinal cord and brain is common and important in goats² and sheep,^{3,4} and CNS disease is encountered sporadically in a wide range of animals including llamas,^{5,6} reindeer, antelope,⁷ caribou, and moose that graze contaminated pastures. Clinical deficits are usually referable to the pelvic limbs, sometimes involve the thoracic limbs also, and may be asymmetrical. An initial impression of a stiff or lame gait progresses to paraparesis or tetraparesis with ataxia. Occasionally, clinical signs reflect cerebellomedullary migration. Cerebral signs are lacking, and affected animals are invariably bright and alert; although often recumbent, they will eat if given access to food. A CSF examination is often informative, with elevated protein levels and a pleocytosis of mononuclear cells and eosinophils.^{2,5,8} Eosinophils may account for most of the nucleated cells, a finding highly suggestive of a parasitic encephalomyelitis. Erythrocytes are often also present in the sample and reflect parenchymal hemorrhage. Following experimental infections in goats and deer, *P. tenuis*-specific IgG could be detected in CSF.⁹ The clinical course is variable with a generally poor prognosis. Modern anthelmintics with larvicidal activity may be beneficial, but some untreated sheep and goats improve spontaneously.

In animals that come to necropsy (often necessitated by paralysis), there are often gross changes to be found. Small hemorrhages may be seen in the spinal leptomeninges. Cross-sections of the spinal cord reveal randomly distributed pinpoint brownish hemorrhages in the parenchyma. Sometimes there are areas of palpable softening with a grayish discoloration of the funiculus. Rarely the parasite will be seen as a green discoloration. Microscopic changes produced by larval migration in the CNS incite a fairly stereotyped response. This description for *P. tenuis* in ruminants is applicable to the injury that other helminths incite in the neuraxis in other animals. The wandering parasite produces

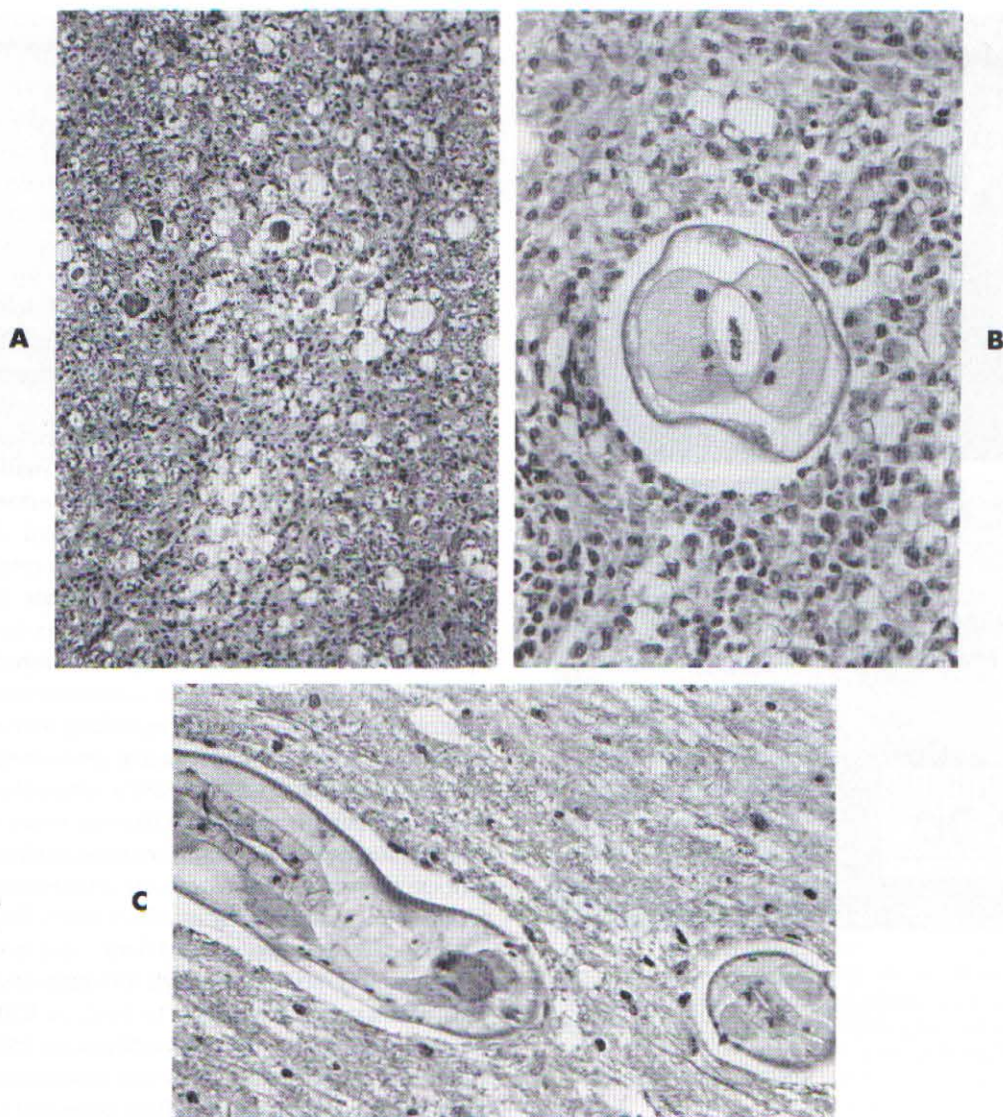


Fig. 3-52. Verminous encephalomyelitis. **A**, Tract of degeneration with swollen myelin sheaths and spheroids, spinal cord, sheep. **B**, *Parelaphostrongylus tenuis* in spinal cord, sheep. (H&E, $\times 350$.) **C**, *Baylisascaris procyonis*, prairie dog brain. (H&E, $\times 350$.)

a tract of disrupted and necrotic tissue; both gray and white matter areas are affected, but myelinated tissue is more commonly involved. Some hemorrhage occurs into the tract, but it is rarely massive unless a large vessel is ruptured. The tract liquefies and attracts macrophages that migrate in, ingest debris, and are progressively converted to swollen gitter cells. Degenerative and reactive changes are marked at the tract margins with many swollen eosinophilic axons (spheroids), ballooned myelin sheaths, and some loss of myelin (Fig. 3-52, A). Hematogenous inflammatory cells are conspicuously sparse. In a few days, a reactive astrogliosis is evident, and some small tracts, not large enough to cavitate, are scarred over. Neighboring blood vessels are cuffed with a few lymphocytes, plasma cells, and occasional eosinophils, and similar cells populate the leptomeninges in

a patchy fashion, the source of the cells commonly found in CSF samples.

Definitive diagnosis of the specific parasitism depends upon finding and identifying the culprit. For some helminthoses, the larvae can be identified by the naked eye (perhaps with the assistance of a dissecting microscope). Parasites may be found within lesion areas, sometimes bathed in a sea of necrotic tissue, eosinophils, and macrophages (Fig. 3-52, B). It is common in paraffin sections to encounter parasites in lesion-free areas (Fig. 3-52, C), which can be explained as follows: After euthanasia of the host, removal and immersion of the CNS tissue in formaldehyde solution is a noxious stimulus to viable larvae, triggering their further migration in the neuroparenchyma until their death by the fixative. It should be noted that it is common to fail to

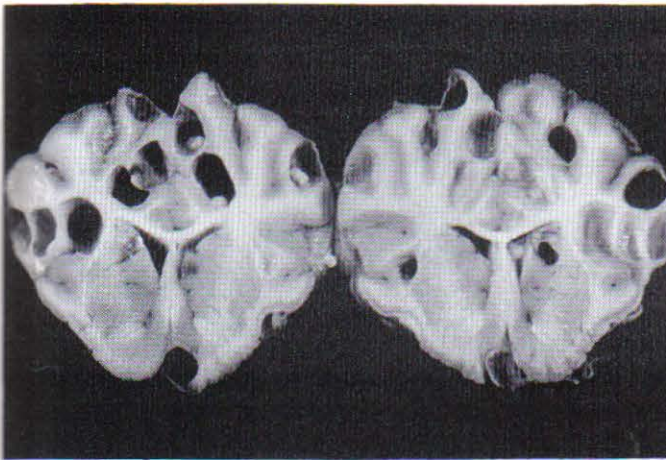


Fig. 3-53. Multiple *Cysticercus cellulosae* cysts within pig brain. White nodules within cysts are scolices.

demonstrate helminth larvae within the CNS. However, the clinical presentation (often as a flock problem), results of CSF examination, and histopathological changes together permit a presumptive diagnosis of cerebrospinal parasitism to be made. The reindeer parasite *Elaphostrongylus rangiferi* can produce cerebrospinal nematodiasis in sheep and goats,^{10,11} which is similar to *P. tenuis* infection. In elaphostrongylosis, inflammatory and degenerative lesions in the spinal roots are common.

Damage to the neuroparenchyma seems to be largely mechanical, but there may be the added effects of toxic larval secretory products. Vascular compromise and ischemia are rarely evident except perhaps in *Cuterebra* infestation (as noted later in this section).

Setaria digitata is a microfilarial worm of cattle that lives in the abdominal cavity of this species. Infection of cattle is recorded in many countries. Transmission is by mosquitoes, and infection of horses, goats, sheep, and camels can also occur. In Sri Lanka, India, Japan, Korea, and Israel, involvement of these aberrant hosts results in a cerebrospinal nematodiasis.¹² Clinical signs are of paresis and ataxia.

In sheep and occasionally other animals, larvae of the canine tapeworm *Taenia multiceps* produce a neurological disease referred to as **gid**. The pathology is twofold, at first associated with the migratory phase of the larval stage, *Coenurus cerebralis*. Necrosis and inflammation in the CNS may be extensive,¹³ visible grossly as yellow to reddish tracts penetrating the parenchyma of the brain. Microscopically, a central core of coagulation necrosis merges into some free blood and ghost cells, degenerate granulocytes, histiocytes including giant cells, mononuclear cells, and a fibroblastic contribution from the meninges. Parasite larvae may be evident within some tracts.¹⁴ The second stage results from the stationary, expanding "bladder worm." Neural tissue is compressed to the point of obliteration by the fluid-filled cyst, and the overlying skull may be thinned or per-



Fig. 3-54. Hemorrhagic tract from strongyle migration, cerebellum, horse.

forated. Attempts to localize the coenurus based on neurological changes in affected sheep are reported.¹⁵ The majority of cysts are located in the cerebrum,¹⁵ and this is reflected by visual loss, circling, and head pressing.¹⁶ In affected sheep, radiology is useful to localize the coenurus.¹⁷ *Coenurus* cysts have been observed in the brains of cats,^{18,19} are nicely demonstrated by computed tomography,²⁰ and may actually be larvae of *T. serialis*.²¹

In **swine**, and sometimes humans, **cysticercosis** is a cause of neurological disease (Fig. 3-53).²² The larval stage is *Cysticercus cellulosae*, the metacestode form of the human tapeworm *Taenia solium*. In pigs, most cysticerci encyst in striated muscle, and the life cycle is completed when inadequately cooked pork is consumed. In humans, identification of the cysts can be made with a high degree of precision by magnetic resonance imaging, which facilitates surgical intervention.²³ Similar studies, employing computed tomography, are reported of porcine cerebral cysticercosis.²⁴ Human cerebral cysticercosis occurs worldwide but with particular frequency in South America, India, and Mexico, and it is the most common parasitic infection of the CNS in humans.^{25,26}

In **horses**, sporadic episodes of profound neurological disease result from the migrations of strongyle larvae, probably *Strongylus vulgaris*,²⁷ within the brain. Larval migration occurs typically in the cerebellomedullary area, producing hemorrhagic tracts of necrosis (Fig. 3-54) and, commonly, severe vestibular disturbance. Cerebrospinal nematodiasis in horses caused by filarii nematodes (*Setaria*

sp., *Halicephalobus* [*Micronema*] *deletrix* (Fig. 3-55) occurs in some areas of the world but is not commonly recognized in North America.^{28,29} Rare episodes of CNS migration by the cattle fly bots *Hypoderma bovis* or *H. lineatum* have been recorded in the horse^{30,31} and even in humans.³² Treatment of bot-infested cattle may kill larvae of *H. bovis* located within the spinal canal and the ensuing inflammatory reaction can produce transitory signs of ataxia.³³

In dogs and cats, cerebrospinal helminthosis is uncommon, save for one or two syndromes (noted later in this section), and invasion into the CNS of carnivores by other parasites is rare. The canine roundworm *Toxocara canis* is an important cause of morbidity in young children; larval wanderings are mainly in thoracoabdominal organs in this syndrome of "visceral larva migrans." Any CNS involvement is unusual,³⁴ although ocular disease is less rare. During the 1980s, the raccoon roundworm *Baylisascaris procyonis* (and, to a lesser degree, *B. columnaris* of skunks) has emerged as an important cause of cerebrospinal nematodiasis in North America.³⁵ Spontaneous or experimental infection in a large number and variety of species, including the domestic dog,³⁶ prairie dogs,³⁷ rabbits,³⁸ pheasant,³⁹ cockatiel,⁴⁰ subhuman primates,⁴¹ and also humans, has been reported. The epidemiology of this infection often relates to animals kept in cages that had previously housed raccoons and were presumably contaminated with *B. procyonis* eggs. The neural lesions in all affected animals are quite stereotyped with extensive tracts of necrosis and microcavitation in the neuroparenchyma. The larvae of *Baylisascaris* are much larger than those of other ascarids, such as *Toxocara canis*,³⁸ and so their wanderings produce extensive tissue destruction. In Australia, the rat metastrongylid *Angiostrongylus cantonensis* is a cause of paraparesis and ataxia in dogs, which, in severe infections, progresses to tetraplegia.⁴² Affected pups show extreme pain if the lumbar area is palpated or manipulated. Examination of CSF reveals an eosinophilic pleocytosis. *Angiostrongylus vasorum*, a parasite of dogs and wild carnivores, has been recorded as a cause of neurological disease in the dog.⁴³ A CNS angiostrongylosis in two foals has also been reported.⁴⁴

The filariid helminth *Dirofilaria immitis* is most frequently a parasite of the dog and cat; adult parasites normally reside in the right side of the heart and the pulmonary arteries. On rare occasions, aberrant migration in the CNS of these two species is encountered,^{1,45} and cerebral infarction, subsequent to arterial occlusion, has been recorded.⁴⁶

Dogs and cats in North America are among the hosts of the dipteran (fly) parasite *Cuterebra*,⁴⁷⁻⁴⁹ and myiasis may occur in the pharynx, upper respiratory tract, and CNS. Neurological disease is variable, depending on the pathway of larval migration. In cats, acute cerebral signs including aggressive behavior, circling, depression, and seizures may mimic the feline ischemic encephalopathy.⁴⁷ The CSF samples from these patients may show a predominance of neu-

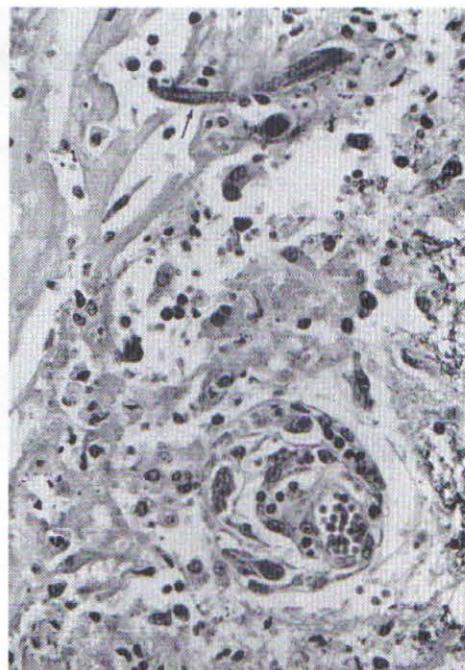


Fig. 3-55. *Halicephalobus deletrix* encephalitis, medulla, horse. Arrow indicates larva. (H&E, $\times 350$.)

trophils,⁵⁰ probably a response to the extensive necrosis. Sometimes at necropsy of these cases, the larval dipteran is found within the leptomeninges or in a hemorrhagic tract (Fig. 3-56). The parasite can be identified under the dissecting microscope or in sections of the tissue by virtue of its cephalic hooks and circumferential rows of spines attached to the cuticle. Tissue injury is usually considerable, and laminar cortical necrosis has been observed,⁴⁷ which may incriminate vascular injury as one mechanism by which the parasite produces malacic change. We have observed a few cases of cerebrocortical necrosis in cats accompanied by an infiltrate of eosinophils; parasites have not been observed, but these also may be cases of *Cuterebra* infestation.

The route of entry of the fly larvae into the CNS has been argued; suggested avenues include the foraminae of the skull (especially the foramen magnum), the ethmoid bone, open skull sutures (in young pups and kittens), and the middle ear.

References are on page 185.

PROTOZOAN ENCEPHALOMYELITIS

The many genera of the phylum Apicomplexa include *Toxoplasma*, *Hammondia*, and *Sarcocystis*. Differentiation of these coccidian parasites in tissue by light microscopic examination may be very difficult if not impossible. Until at least the 1960s, sporozoan parasites observed by histopathologists in association with tissue injury in (among other organs) lymph nodes, lung, muscle, and CNS of animals and humans and in abortuses were presumptively identified

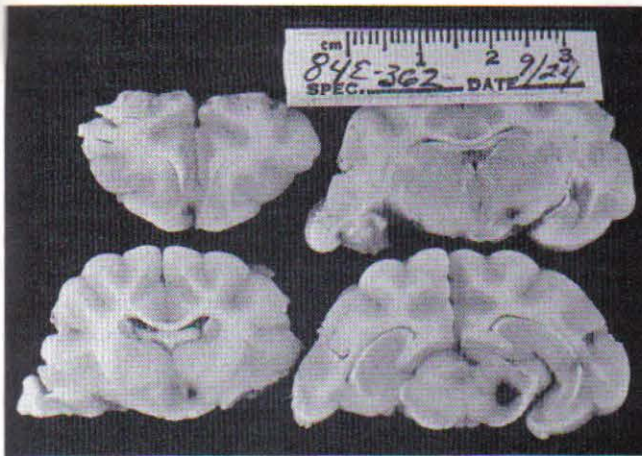


Fig. 3-56. Hemorrhagic tract from *Cuterebra* migration through brain, domestic cat.

as *Toxoplasma gondii*. It is now evident that pathogenicity is not confined to this single genus. Early reports of CNS toxoplasmosis in horses were almost certainly cases of equine protozoal myeloencephalitis (discussed later in this section), which currently is ascribed to *Sarcocystis* infection. That all cases of protozoan encephalomyelitis in the dog are due to toxoplasmosis has been challenged by Bjerkås and Dubey, and the existence of a new organism (*Neospora caninum*) proposed.^{1,2} The same query can be addressed to cerebral toxoplasmosis in humans, now common in HIV infection. Episodes of protozoan radiculoneuritis in young dogs (Chapter 7) were commonly seen in the face of negative serological tests for *Toxoplasma*. Hence we must anticipate that where episodes of spontaneous disease were described, the literature contains many erroneous diagnoses of toxoplasmosis; it will not be surprising if there are further revelations in the future.

Toxoplasma, Neospora, and Sarcocystis

Toxoplasma gondii is a coccidian parasite for which the cat is the definitive host.^{3,4} It appears that any warm-blooded animal may act as an intermediate host, and infection is remarkably ubiquitous.^{5,6} The coccidian enteroepithelial cycle occurs in the small intestine of domestic cats and other Felidae, and oocysts are shed in the feces. The extraintestinal cycle, following dissemination to many organs, occurs in intermediate hosts, which may include humans, other mammalian species, and birds. Cats may also be infected by the extraintestinal phase, thus having the distinction of acting as both intermediary and definitive hosts. Infection occurs by one of three pathways: (1) by ingestion of tissue (meat) containing tissue cysts, (2) following the ingestion of food contaminated with sporulated oocysts from cat feces, and (3) by infection in utero. The acute systemic infection often passes unnoticed except for transplacental infection of the fetus, which may be devastating. Most common in humans,

this congenital form of toxoplasmosis is associated with a severe encephalitis with cerebral calcification, hydrocephalus, microcephaly, and chorioretinitis.^{7,8} In animals, fetal infection appears to be most common in sheep. There is a primary placentitis affecting the cotyledons, with further seeding of the organisms to the fetal lamb. The pregnancy is frequently aborted late in its course, with tissue cysts sometimes found in the fetal brain and myocardium.^{6,9} The fetal lamb brain may also show a multifocal leukoencephalomalacia of the rostral cerebral white matter.^{9,10} Mineralized necrotic tissue may be evident grossly as pinpoint, chalky white foci. This apparently is a consequence of placentitis, placental insufficiency, and subsequent fetal hypoxia during the pregnancy.¹¹

Following the acute infection in intermediate hosts, tissue cysts form, predominantly in the CNS and skeletal and heart muscle.⁵ At this chronic stage of the infection, the organism is largely intracellular (within neurons and muscle cells), a locale that offers both nutritional and immunological advantages to the parasite. Chronic infection may persist for the life of the host, and very rarely (usually in the cat) will one encounter encysted organisms as an incidental finding in CNS sections. There is evidence that cysts may survive subclinically in the human brain also.¹² The conversion from the acute, destructive infection to a chronic, inactive one coincides with the development of host humoral and cellular immunity. The corollary of this statement is that latently infected hosts are susceptible to reactivation of their toxoplasmosis by severe immunosuppressive disorders.¹³ Association of toxoplasmosis with canine distemper encephalomyelitis, a *Morbillivirus* infection in dogs, has been recognized for decades. In humans, many patients with HIV infection succumb with cerebral toxoplasmosis.¹⁴⁻¹⁶ Clinical toxoplasmosis is thus to be anticipated in young animals, particularly if the infective dose is heavy, and in immune-compromised mature animals. The active infection is often disseminated, most commonly involving the CNS, lung, myocardium, liver, pancreas, striated muscle, and lymph nodes; predilection varies with the host species. In humans, for example, toxoplasmosis is a well-recognized cause of lymphadenopathy.¹⁷ In cats, severe interstitial pneumonia is common,¹⁸ whereas in dogs concurrent polymyositis and encephalomyelitis are a common scenario.¹⁹ Curiously, in puppies and young dogs, polyradiculoneuritis is a common pattern (see Chapter 7). To reiterate, that all these protozoan infections are caused by *T. gondii* is now not accepted²⁰⁻²² based on the results of serological, immunocytochemical, and ultrastructural studies. The discussion that follows often presents various features of what has been published as "toxoplasmosis," but this should be viewed generically as protozoan disease.

Our focus in this volume is the nervous system, and protozoan encephalomyelitis caused by *T. gondii*, *Neospora caninum*, and perhaps other organisms is encountered most commonly in the **dog** and the **cat**. Clinical signs suggest

focal or multifocal disease and may reflect injury to cerebral, brain stem, cerebellar, or spinal cord areas or combinations of these. Accordingly, excitability or depression, seizures, head tilt, ataxia, paresis, and paralysis are all possible presentations. Involvement of spinal cord gray and white matter may produce a mixture of lower and upper motor neuron signs in different limbs. Polymyositis also is common, particularly in the dog. There may be systemic illness with respiratory difficulties and diarrhea.²³ The CSF changes to be anticipated are elevated protein levels and a mixed pleocytosis of macrophages, neutrophils, and lymphocytes. An eosinophilic pleocytosis was observed in eight dogs, one of which was found at necropsy to have a protozoal encephalitis and myositis, which were suspected in a second;²⁴ others of the group, however, were thought to be manifestations of a novel syndrome. In some protozoal infections, the peripheral blood may show an eosinophilia.¹⁹ In the dog, clinical differentiation from canine distemper encephalomyelitis may be very difficult; pure toxoplasmosis of the canine CNS is much less common than CDE. Toxoplasmosis is well recognized as occurring as a secondary event in dogs and other carnivores with primary CDE,^{25,26} although for some reason this seems to be less common now than in decades past. In hares, latent toxoplasmosis may show recrudescence after pseudotuberculosis.²⁵

At necropsy, there is a nonsuppurative meningoencephalomyelitis affecting gray and white matter. A periventricular pattern is occasionally seen in young animals with acute disease, and this may be evident grossly as roughening and brownish discoloration in subependymal areas of the brain. Peracute infections produce hemorrhagic-necrotic foci. Chronic focal infections may show areas of discoloration and swelling, as well as loss of gray-white boundaries. Lesions may be focal or multifocal and are often locally extensive.

The sequential evolution of the CNS lesions in experimental toxoplasmosis has been studied in several species by Koestner and Cole.^{23,27,28} They describe a common theme of early vasculitis, necrosis of the adjacent neuroparenchyma with free organisms in the tissue, and a mixed polymorphonuclear-mono-nuclear cell response. As lesions progress through subacute to chronic stages, focal microgliosis becomes more evident, necrosis diminishes, organisms in tissue cysts appear, and the cellular response becomes more purely mononuclear. The histological findings thus vary with the stage of the encephalomyelitis that is examined. Chorioretinitis often accompanies CNS infection and is evident ophthalmoscopically and histologically.

In the natural disease, microscopic changes predominate in gray matter. In the early infection (usually not observed in natural disease), there is capillary endothelial necrosis with actively proliferating, free, crescent-shaped tachyzoites (endozoites) in the vessel wall, perivascular space, and adjacent neuropil. Necrosis may be extensive, particularly in congenital infections and perhaps also depending upon the

strain of the organism. Individual cell lysis is a consequence of intracellular replication of tachyzoites and subsequent cell rupture, but vascular injury is probably involved in producing larger areas of necrosis. An inflammatory response develops in the overlying leptomeninges and as perivascular cuffs in the neuroparenchyma; adventitial cell proliferation thickens blood vessels. Infiltrating cells are neutrophils, monocytes, and a few lymphocytes. The adjacent white matter is edematous and may be involved by extension of inflammation from gray matter. Necrosis of neurons, sometimes showing ischemic change, and of glial elements triggers a focal nodular microgliosis. With time, the accumulation of lymphocytes and monocytes in the tissue imparts a more granulomatous appearance, and necrosis diminishes. Organisms are now more readily found at the margins of lesions, ingested within macrophages, and in tissue cysts (Fig. 3-57). The dormant, tissue cyst dweller is a bradyzoite (or cystozoite), whereas that within a parasitophorous vacuole is a tachyzoite (endozoite). Some cysts are found in normal CNS tissue, perhaps carried there in histiocytes. Plasma cells appear in the perivascular cuffs, and granulocytes decline. A reactive astrocytosis is found admixed with the hematogenous cells.

The identification of free tachyzoites in CNS paraffin sections is notoriously difficult (bar the occasional fortuitous case), and they may be more readily identified in stained squash preparations.^{14,25} Tissue cysts are much less of a problem. Immunofluorescence and immunocytochemical techniques can help in the search for parasites,^{8,21} and ultrastructural studies of the organism in natural and experimental infections have been described.^{5,21,29,30} The number and location of subcellular organelles, which include the nucleus, apical conoid, polysaccharide granules, rhoptries, and micronemes, can be used to distinguish the tachyzoite from the bradyzoite and *Toxoplasma gondii* from other species.^{21,22,31}

In 1984, Bjerkås and colleagues²⁰ reported a cyst-forming sporozoan agent that caused encephalomyelitis and myositis in six young dogs. On the basis of negative serology for toxoplasmosis, ultrastructure of the organism, and its pattern of transmissibility, they concluded that the organism probably was not *Toxoplasma*. More extensive ultrastructural studies of the tachyzoites and bradyzoites showed that they harbored numerous rhoptries—many more than other known cyst-forming coccidia contain—and immunocytochemically the organisms were unreactive with anti-*T. gondii* serum.³² In a retrospective study of 23 cases of canine "toxoplasmosis," Dubey and his colleagues¹ identified what is most likely the same protozoan agent.³³ They reclassified 10 of the cases and named the organism *Neospora caninum* (to be distinguished from *T. gondii*). Most of the 10 cases involved CNS and muscle, and so it is highly probable that many previously diagnosed cases of protozoan encephalomyelitis and myositis in dogs (and probably some other species) are neosporosis. By light microscopy, *Toxoplasma*

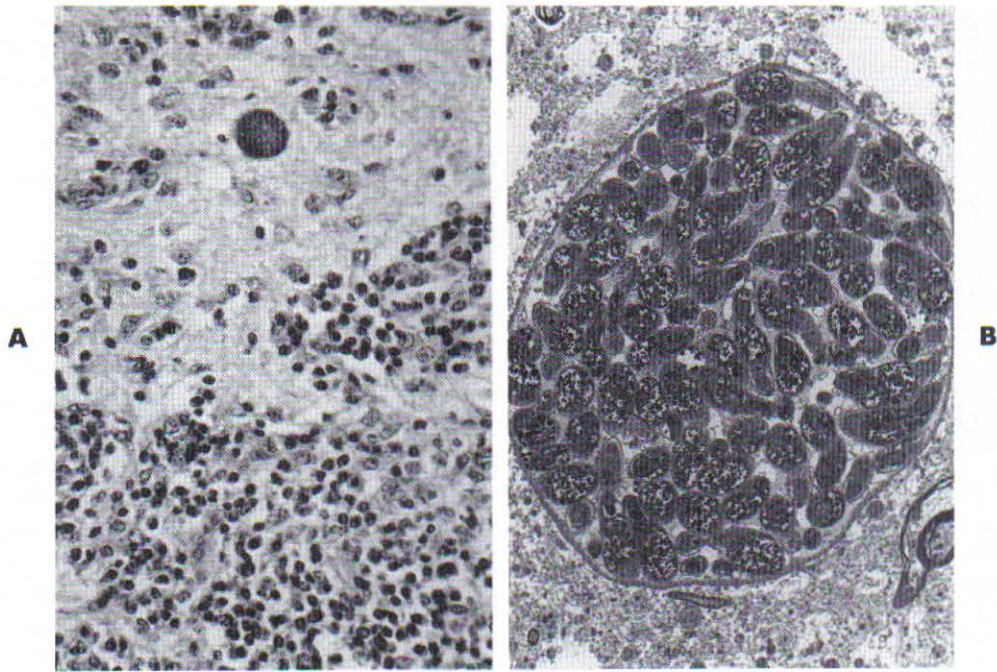


Fig. 3-57. Protozoan encephalomyelitis, dog. **A**, Nonsuppurative encephalitis with tissue cyst, cerebrum. (H&E, $\times 350$.) **B**, Ultrastructural features of a *Toxoplasma gondii* cyst within the cerebral cortex, dog. ($\times 3,850$.)

and *Neospora* cannot be differentiated, but ultrastructurally and immunohistochemically³⁴ the two are distinct. Isolation of *N. caninum* in tissue culture and its transmission to mice, dogs, and cats were reported,^{35,36} including transplacental infection in the dog.³⁷ Retrospectively, cases of protozoan encephalomyelitis in the dog³⁸ and in other species (see later in this section) have been ascribed to *Neospora*. Its life cycle, natural mode(s) of transmission, and host range are to be established,³⁹ and the role of *T. gondii* as a cause of neurological disease in the dog, cat, and other species must be re-evaluated.

Toxoplasmosis is important in **sheep** and **goats**, in which species abortion and perinatal deaths can produce significant losses. Systemic disease with encephalomyelitis in adult sheep is probably sarcocystosis, whereas in mature goats, *T. gondii* is still incriminated.⁴⁰ In **cattle**, episodes of a systemic protozoan infection with fever, anemia, lymphadenopathy, wasting, abortions, and high mortality were, as suspected, probably not toxoplasmosis but rather sarcocystosis.⁴¹⁻⁴⁴ Encephalitis and myositis were common observations at necropsy. Of 445 aborted bovine fetuses examined over a 2-year period in diagnostic laboratories, 18% had evidence of protozoan encephalitis, myocarditis, and hepatitis.⁴⁵ Munday and associates⁴⁶ described two cases of *Toxoplasma* encephalitis in aborted calves; that they were *Sarcocystis* or *Neospora* infection seems highly likely. Dubey⁴⁷ proposes that all reports of bovine neonatal toxoplasmosis were probably misdiagnoses.

Protozoan encephalomyelitis occurs only sporadically in cattle and sheep (in contrast to the horse) but is recognized in several countries (Fig. 3-58). In recent years, many cases have been reported as putative *Sarcocystis* encephalomyelitis, based on the schizogenous stage of the organism.⁴⁸ In sheep, reports have described lambs with varying combinations of ataxia, paresis, and paralysis;⁴⁹⁻⁵¹ the clinical course is usually progressive. Pathological findings are only microscopic and consist of a nonsuppurative meningoencephalomyelitis that may be severe. Microglial nodules and perivascular cuffs of mononuclear cells are disseminated in gray and white matter, and focal areas of necrosis, particularly in the spinal cord, are common. Organisms, often schizonts with merozoites, are found within astrocytes and neurons and free in the tissue. Hartley and Blakemore⁴⁹ provide the ultrastructural details of the organelles and their disposition within the merozoite stage. Dubey and associates,⁵² showing commendable enthusiasm, re-examined case 1 from Hartley and Blakemore's report 22 years after the necropsy was performed and, on ultrastructural grounds, suggested that the organism is a *Sarcocystis*. Consistent with this tentative classification is the concurrent presence of mature cysts in striated muscles in some cases; this has been supported in other cases on immunocytochemical grounds.⁵³ Experimental infection of lambs with an ovine *Sarcocystis* produced anemia, myositis, and nonsuppurative encephalomyelitis; second-generation meronts and sarcocysts could be identified by immunocytochemistry.^{54,55}

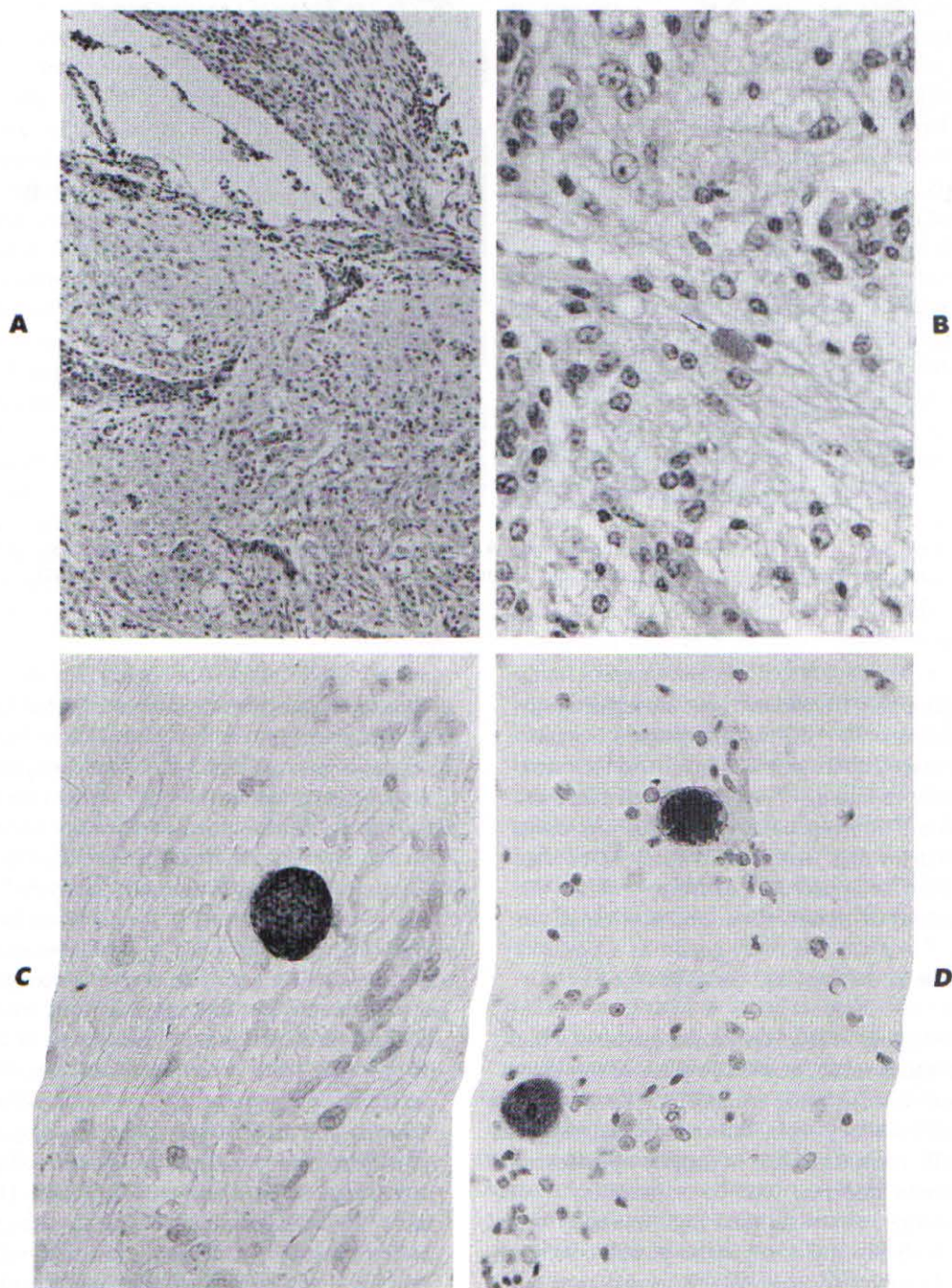


Fig. 3-58. Protozoan encephalomyelitis. **A**, Myeloradiculitis, calf. (H&E, $\times 140$.) **B**, *Neospora caninum* cyst in medulla (arrow), same calf as **A**. (H&E, $\times 560$.) **C**, *N. caninum* in calf spinal cord. (Immunocytochemistry, $\times 560$.) **D**, *Toxoplasma gondii*. Encysted organisms in cerebrum of a lamb shown by immunocytochemistry. ($\times 560$.)

Dubey and colleagues⁵⁶ described encephalitis caused by a *Sarcocystis*-like organism in an 18-month-old Hereford steer. The animal had become ataxic, recumbent, and blind. Schizonts with merozoites were found within a multifocal granulomatous meningoencephalitis. A further case in a calf that succumbed soon after birth⁵⁷ was probably a congenital infection. In these cases, the form of schizogony, the presence of schizonts in vascular endothelial cells, and the disposition of organelles as seen by electron microscopy provide evidence in favor of a classification in the genus *Sarcocystis*. The definitive host is presumed to be a carnivore, which could include the domestic dog, foxes, coyotes, wolves, lynx, and perhaps others. In a congenital protozoan encephalomyelitis in a Friesian calf,⁵⁸ ultrastructural features of the merozoites were consistent with *T. gondii*, but the cysts were unreactive immunohistochemically with anti-*Toxoplasma* serum and only weakly positive with an anti-*Sarcocystis* serum. A similar condition in newborn calves was reported by Parish and associates;⁵⁹ re-evaluation of both cases suggests that they are *N. caninum* infections.^{47,60}

In the United States^{61,62} and Canada,⁶³ a protozoan encephalomyelitis of the horse (EPM) is well recognized. Cases have been reported from Brazil.⁶⁴ Initially described as equine CNS toxoplasmosis (or *Toxoplasma*-like),^{65,66} the agent is currently of uncertain classification but is thought not to be *T. gondii*. It is probably a member of the genus *Sarcocystis* and the name *S. neurona* has been proposed.⁶⁷ Immunoblot studies have shown *S. neurona*-specific proteins that should permit specific serodiagnosis.⁶⁸

Although EPM is seen in many horse breeds,⁶⁹ when case prevalence is compared with hospital populations, Standardbred horses appear to be over represented.⁷⁰ This may reflect their increased susceptibility or, more likely, greater exposure to the agent. Clinical disease in horses and ponies with EPM is extremely variable, reflecting possible involvement anywhere in the neuraxis, both gray and white matter. Spinal cord disease is most common, is often asymmetric, and affects both gray and white matter. Although lesions can occur anywhere in the spinal cord, there appears to be a preference for the cervical and lumbosacral intumescences. An asymmetrical lesion of the cervical intumescence produces a hemiparesis with lower motor neuron signs (gray matter lesion) in the affected forelimb and upper motor neuron signs and proprioceptive deficits (white matter lesion) in the ipsilateral pelvic limb. Occasionally a chronic lesion may localize in just one area of the ventral gray column, causing lower motor neuron signs with severe denervation atrophy (e.g., of the gluteal muscles). Brain lesions are most common in the pons and medulla, where they cause ataxia with general proprioceptive deficits and/or disturbances of the vestibular system. The latter also causes a head tilt with the balance loss. This is accompanied by spastic hemiparesis or tetraparesis and cranial nerve involvement: facial paresis, dysphagia, and jaw and tongue paresis. Involvement of the trigeminal or hypoglossal motor



Fig. 3-59. Equine protozoan myeloencephalitis. **A**, Bilateral lesions in the motor nuclei of the trigeminal nerve, pons. **B**, Lesion in medulla.

nuclei in the brain stem may be exquisitely discrete and can result in selective asymmetrical (ipsilateral) atrophy of the masticatory muscles or of the tongue. Rarely, lesions at one site develop, peak, and resolve to be followed some time later by a second bout of acute neurological disease referable to a second neuroanatomical lesion.

At necropsy, gross pathological changes in the CNS are common and may be focal and localized or widely disseminated. Pons, medulla, and spinal cord are most often the sites of lesions (Fig. 3-59), but they may occur more rostrally in the brain. The intact brain and spinal cord are unremarkable or perhaps slightly swollen, but transverse sections reveal a yellowish brown discoloration that may be red if fresh hemorrhage is present. Microscopic study shows a prolific, often necrotizing, nonsuppurative meningoencephalomyelitis. Spinal cord involvement is perhaps most consistent (and for this reason we prefer the designation myeloencephalitis). In affected segments, the perivascular spaces and leptomeninges contain many lymphocytes, a few plasma cells, macrophages, and consistently eosinophils, which constitute a minority population but are readily found.

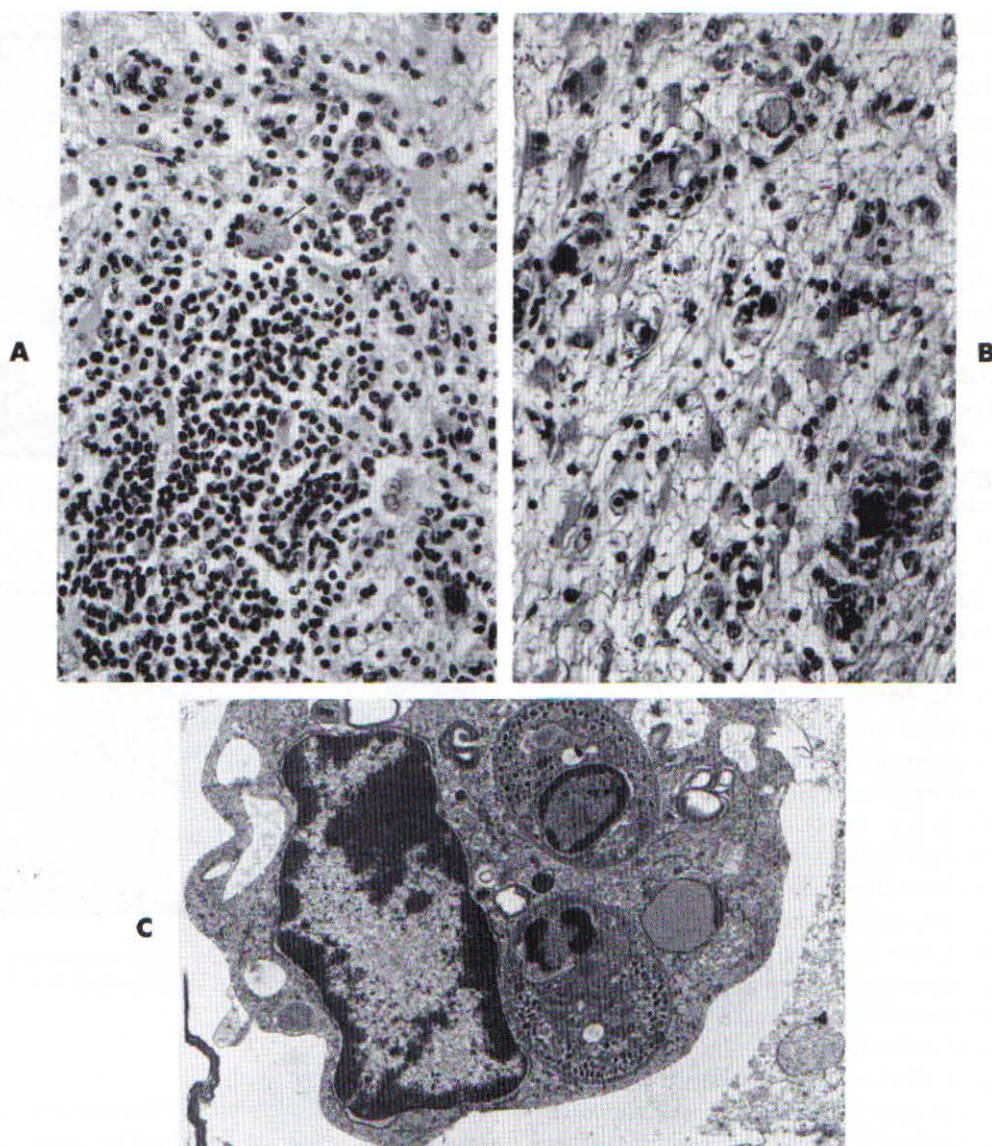


Fig. 3-60. Equine protozoal myeloencephalitis. **A**, Heavy lymphocytic inflammation and giant cell formation (arrow), medulla. (H&E, $\times 350$.) **B**, Chronic inflammation in spinal cord ventral horn has destroyed neurons; astrocytic scar and a few lymphocytes remain. (H&E, $\times 350$.) **C**, Electron micrograph of *Sarcocystis neurona* in a macrophage. ($\times 12,500$.)

These inflammatory cells are found within the tissue, where sporadic numbers of giant cells are also encountered (Fig. 3-60, A). In the gray matter, neurons and neuropil show degenerative changes that may progress to necrosis. Involvement of white matter produces a vacuolar change, which is accompanied by a moderate, diffuse astrocytosis and small knots of glial cells, probably microglia. Areas of necrosis may be extensive in gray or white matter and will liquefy and incite a histiocytic response. Protozoan organisms occur within the lesion but are frequently difficult to find; they are identified in approximately a third of the cases of EPM that we see and typically are lacking in horses that have received specific therapy (folic acid antagonists).⁷⁰

Their routine detection in cases in the older literature may relate to the fact that these horses were often treated with corticosteroids (especially so if the doses were high and the treatment prolonged). Unfortunately for identification purposes, PAS, silver, and Giemsa stains do not offer any advantage over routine H&E-stained sections, but schizonts and merozoites can be identified immunohistochemically with antisera to *S. cruzi* or *S. neurona*.^{67,71} Oval to crescent-shaped organisms may be found singly, in clusters, or in rosettes within macrophages, glial cells, neurons, or the wall of blood vessels.^{62,63,72} Free organisms occur in the neuropil in areas of necrosis but must be differentiated from cellular debris.

Old "burned-out" lesions in the motor nuclei in the brain stem and spinal cord ventral gray matter have a conspicuous loss of neurons, which are replaced by reactive astrocytes (Fig. 3-60, B). This pattern is accompanied by an ipsilateral Wallerian degeneration in the cranial nerve or ventral nerve roots and spinal nerve, with atrophy of the innervated muscle (gluteal, masseter, and so on). Ultrastructural features of the organism (Fig. 3-60, C) and its mode of division have been described.^{63,73}

Evidence has accumulated that reduces the probability that this is a *Toxoplasma* infection. The organism lacks the histochemical properties of *Toxoplasma*,⁶³ and ultrastructural features of the pattern of asexual reproduction (schizogony) are more consistent with a *Sarcocystis*.^{73,74} However, extensive attempts to fulfill Koch's postulates in horses with several species of *Sarcocystis* have so far been unsuccessful.⁷⁴ With its selective involvement of motor nuclei in the brain stem (rarely) and its frequent attack upon motor neurons of the cervical and lumbar enlargements (common), a pattern of CNS invasion along peripheral nerves from skeletal muscle can be hypothesized. In this sense, *Sarcocystis*, a coccidian known to reside in striated muscle, would seem a reasonable candidate.

Although CNS toxoplasmosis in **pigs** is described,²⁸ most infections are subclinical. Experimental infections have been described in laboratory rodents, particularly the **mouse**, which has been used for recovery and propagation of the organism. Experimental murine infections show a marked tropism for gray matter by the actively replicating tachyzoite (endozoite) and particularly the tissue cyst stages.⁵ Proliferative forms of the organism were observed extracellularly and within parasitophorous vacuoles within various neural cells and in macrophages and neutrophils. In contrast, tissue cysts, containing bradyzoites (cytotozoites), developed almost exclusively in neurons,⁷⁵ which showed no degenerative changes and had not attracted an inflammatory reaction. Tissue cysts expand because of division (endodyogeny) of bradyzoites, this occurring in the first 1 to 3 months of cyst formation.

Encephalitozoon

Encephalitozoon cuniculi is an obligate, intracellular microsporidian parasite of several animal species including humans. First described in rabbits in the 1920s, the organism for some years was transferred to the genus *Nosema*, and the infection was thus known as nosematosis. Based on ultrastructural examination of stages of the life cycle, however, the mammalian organism has been returned to the *Encephalitozoon* genus. There seems to be but one pathogenic species.

Encephalitozoon cuniculi infection is best known in **rabbits**, where characteristically a clinically inapparent infection is found incidentally in the course of histopathological studies. Occasionally paralysis, tremors, seizures, and death occur.²⁵ The lesions are microscopic and disseminated in

both gray and white matter of the CNS. Focal granulomas form from epithelioid histiocytes (Fig. 3-61, A), and their centers may liquefy. The neighboring leptomeninges and parenchymal blood vessels are infiltrated and cuffed by lymphocytes that also wander into the neuropil and the granulomatous foci. Parasites are found within parasitophorous vacuoles, but free organisms are very difficult to identify in H&E-stained sections. However, spores can be identified by virtue of being gram-positive (Fig. 3-61, B), birefringent,⁷⁶ and smaller than the zoites of *T. gondii*. Granulomatous to nonsuppurative interstitial nephritis is invariably found also, and it seems that the brain and kidney are the main targets for this infection. Lesions in the liver, spleen, and myocardium may also be found. Spores are shed in the urine, an important source of infection for other animals. In **mice**, subclinical infection is again the rule.⁷⁷ The lesions are predominantly of lymphocytic meningoencephalitis, and granulomas are fewer. Infection also occurs in **rats** and **guinea pigs**. Its importance in the laboratory species is mainly where infected animals have unknowingly been used in studies with infectious agents or potential carcinogens. In some studies, from 30% to 50% of animals have had brain lesions in the absence of neurological disease.

Unlike the laboratory animal species, clinical disease and deaths occur in some carnivores, particularly in young animals. Disease in **dogs** is rare in the United States⁷⁸ but is recognized with greater frequency in South Africa,⁷⁹ perhaps indicating strain differences in pathogenicity. The infection in puppies is mainly neurological, with a spectrum of signs ranging from paresis and ataxia to blindness, seizures, and aggressive changes. Clinically, confusion with canine distemper and rabies can occur. Several puppies in a litter may be affected, generally within the first few weeks of life.⁷⁹ The CNS changes are a diffuse granulomatous meningoencephalitis. Vascular changes are prominent with adventitial cell hyperplasia and lymphoid infiltrates in blood vessel walls. Granulomas appear near reactive vessels and are mixed with proliferating astrocytes and microglial cells. Focal fibrinoid necrosis of arteries, particularly meningeal, may be seen.⁸⁰ Collections of organisms within a parasitophorous vacuole are found within neurons, endothelia, and tunica media of arteries and veins. The ultrastructural features of the CNS infection in dogs are described by Van Dellen and associates.⁸⁰ Stages of the life cycle include an early proliferative phase, sporonts, sporoblasts that acquire a coiled filament, and the mature spore. Cerebral vasculitis was evident as an integral element in the disease process.

In Norway, **blue foxes** are raised for commercial purposes and have been found to be highly susceptible to encephalitozoonosis. Clinical disease is seen in young pups around 2 to 5 months of age. It is suspected that clinical disease follows infection in utero. Clinical disease reflects the neurological disorder. Lesions are a disseminated granulomatous meningoencephalomyelitis, particularly involving the cerebral cortex.⁸¹ Infiltrates consist of lymphocytes,

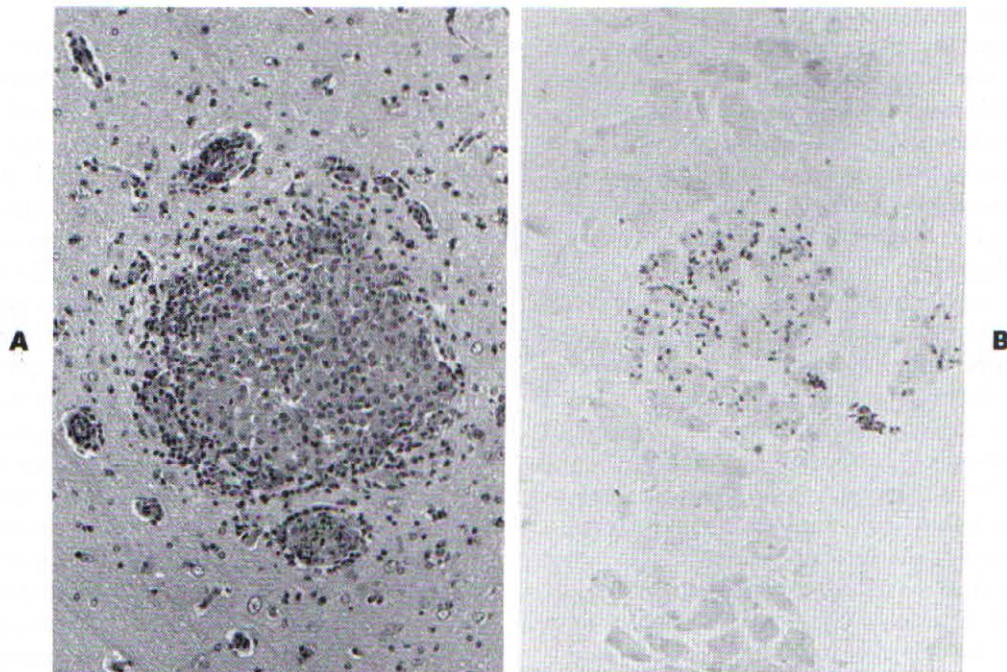


Fig. 3-61. Encephalitozoonosis. A, Granuloma in hippocampus, rabbit. (H&E, $\times 180$.) B, Organisms within a cerebral granuloma shown by Gram stain, mouse. ($\times 560$.)

macrophages, and plasma cells. Vasculitis is prominent and occurs in many organs. Acute vascular changes are necrotizing, but proliferative changes in the subacute to chronic stages may resemble polyarteritis nodosa. Parasites are found within neurons, blood vessels, and macrophages but not astrocytes or oligodendrocytes.⁸² Parenchymal granulomas consist of epithelioid macrophages admixed with a few neutrophils, plasma cells, and lymphocytes. The neuroparenchyma shows degenerative changes, neuronal depletion, and white matter spongiosis. Tissue injury probably results directly from the proliferating organism and indirectly from vascular injury.⁸²

Infection in **primates** is rarely reported but has recently been described in squirrel monkeys.⁸³ Affected monkeys showed few or no specific clinical signs before death. Granulomatous inflammation was prominent in the brain and leptomeninges, kidneys, and other organs. Vasculitis involving multiple organs was common also.

Differentiation of *T. gondii* from *E. cuniculi* may at times present difficulties. *Encephalitozoon cuniculi* cysts are usually larger with ovoid organisms that are smaller than *T. gondii* bradyzoites, which are crescentic in contour. Mature *E. cuniculi* spores are gram-positive and birefringent. Differentiation may be made immunocytochemically²¹ and by electron microscopic examination of stages of their life cycles.^{5,75,80,82}

Trypanosoma

Trypanosomes are important insect-transmitted protozoan parasites that infect humans and many animal species

in large areas of the tropical and semitropical regions of the world. In Africa, *Trypanosoma vivax*, *T. congolense*, and *T. brucei* are important animal pathogens; *T. cruzi* is the cause of Chagas' disease in humans and animals, which occurs particularly in Central and South America. These organisms range from apathogenic to highly virulent and so produce a spectrum of disease syndromes, usually marked by anemia, weight loss and weakness, lymphadenopathy, and dependent edema of the body and limbs. In some trypanosomal infections, signs of neurological dysfunction including ataxia, paresis of limbs, and torticollis are evident.⁸⁴⁻⁸⁶ In horses with dourine (*T. equiperdum*), facial paralysis is common. Where studies of the CNS have been performed, evidence of a predominantly nonsuppurative meningoencephalitis, harboring the parasite, has been found⁸⁷⁻⁹⁰ and is reflected in changes in CSF.^{91,93}

Acanthamoeba and Entamoeba

Amebic meningoencephalitis is well recognized in humans, and a case in a dog, identified by immunofluorescent procedures as *Acanthamoeba castellanii*, has been published.⁹⁴ Areas of hemorrhage and purulent encephalitis harbored trophozoites and cysts. Amebic meningoencephalitis in humans usually follows primary colonic localization (*E. histolytica*), whereas the *Acanthamoeba* group is associated with compromised patients.⁷ In the dog with *A. castellanii* infection, subnormal humoral and cell-mediated immune activity was documented.⁹⁴ A necrotizing meningoencephalitis in a mature Döhhne merino sheep was associated with amebal organisms, believed to be *Acanthamoeba* sp.⁹⁵

Babesia and Theileria

Babesia are tick-transmitted protozoan organisms that parasitize erythrocytes in several species and produce fever, anemia, jaundice, and hemoglobinuria. In cattle, red blood cells parasitized by *B. bovis*⁹⁶ are sequestered in cerebral capillaries, and signs of nervous derangement may be evident with depression, prostration, and seizures. Diagnosis requires examination of brain tissue. *Theileria parva* is the cause of East Coast fever in Africa, a highly lethal disease in non-indigenous cattle breeds. The organism is transmitted by the brown ear tick *Rhipicephalus appendiculatus*. Clinical disease is marked by high fever, lymphadenopathy, ocular and nasal discharge, and, terminally, by severe dyspnea. Occasionally, cerebral theileriosis is seen⁹⁷ with blindness, a staggering gait, abnormal nystagmus, recumbency, opisthotonus, and death. These signs of diffuse brain injury result from the thrombosis or sludging of meningeal vessels with parasitized lymphoblasts and resulting cerebral infarction. Sometimes the brain has a muddy yellowish discoloration, evidence of prior episodes of hemorrhage. Cerebral theileriosis is also associated with *T. mutans*, *T. taurotragi*, and *T. annulata* infection.⁹⁸

References are on page 186.

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Chapter 4 INJURIES TO THE CENTRAL NERVOUS SYSTEM

TRAUMATIC INJURY TO THE CENTRAL NERVOUS SYSTEM

There are many causes of traumatic injuries, and their treatment constitutes an important component of clinical practice. Whereas the attending veterinarian (or physician) is at first concerned with immediate life-threatening impediments—obstruction to air flow, shock and hemorrhage resulting in circulatory collapse, pneumothorax—an evaluation of potential injuries to the neuraxis and its bony encasements must soon follow.¹ This examination must be performed cautiously, as excessive manipulation can exacerbate neural damage.

Central nervous system injuries have **extrinsic** or **intrinsic** causes. The former include automobile accidents, falls, kicks, bites, penetrating objects (commonly bullets), being stepped on or otherwise crushed, and other causes of physical injury. Electrical shocks can produce violent muscular contractions, resulting in vertebral fractures and spinal cord necrosis.² In veterinary medicine, we are rarely if ever presented with forensic cases wherein death allegedly results by intent. In humans, forensic medicine has developed into a discipline in its own right, requiring a combination of conventional pathological expertise, astute observation, and sharp qualities of detection. Some types of injuries affect both man and beast: Falls from high buildings have now been seen with sufficient frequency in the cat to qualify as the "feline high-rise syndrome."³ Other forms of extrinsic injury to the CNS are unique to veterinary medicine, for example, the vertebral fractures occurring in cases of bovine dystocia where forced extraction of the calf is employed.⁴ There are many types of intrinsic CNS injury, including that caused by intervertebral disk prolapse; vertebral malformation; pathological fracture of vertebrae as a sequel to nutritional osteopenia, osteomyelitis, or neoplasia; extramedullary space-occupying lesions (abscesses, neoplasms), and the traumatic damage produced by the many and various

parasites that commonly or infrequently migrate within the brain and spinal cord parenchyma.

It is common experience that severe injury to the CNS leaves permanent, crippling deficits for the remainder of the patient's life. In humans, such range from birth-associated cerebral hypoxia/ischemia (cerebral palsy), to tetraplegia resulting from cervical vertebral fracture or luxation (often caused by motor vehicle accidents and sports activities), to cerebrovascular accidents in the aged. The apparent inability of the CNS to regenerate and reconstitute fiber tracts that have been interrupted, in contrast to the reasonable efficiency with which this can occur in the peripheral system, has both fascinated and frustrated clinicians and investigators for decades. It appears that the milieu of the brain and spinal cord is inhibitory to axonal regrowth, whereas the same nerve fibers extend perfectly well if surgically directed into a PNS environment. Astrocytes have previously been considered one element antagonistic to CNS repair,⁵ but recent investigations point to myelin membrane proteins as important sources of neurite growth inhibition.⁶ In the presence of monoclonal antibodies that neutralize these proteins or in newborn rats x-irradiated to produce a zone of hypomyelination, central axonal regrowth can occur.^{7,8} These observations will no doubt be exploited for possible therapeutic applications.

To resist the everyday stress of activity, the brain and spinal cord are protected by the ligaments in the vertebral canal, meninges, calvaria and vertebrae, overlying muscles, skin, and haircoat. In animals, better-developed temporal muscles and more extensive frontal sinuses probably afford more protection for the brain than is available to human beings. The hollow, domed, bony calvaria is resistant to considerable force, which diffuses over its surface and to the base. Trauma to the skull may result in a basilar fracture, most commonly in the horse. If the impact is sufficiently powerful, the calvaria fractures where it is struck (Fig. 4-

1), just like an egg.⁹ This constitutes one mechanism of brain injury after head trauma, referred to as contact phenomena. The other mechanism relates to accelerating events after impact. Invariably, when brain injuries occur, the head is moving (as in a fall) or is at least mobile. If the head is immobilized, the injury transmitted to the brain is much less than when the head is free. The amount of freedom for the brain to move within the cranial cavity is a second important determinant in the outcome of head injury. For example, in elderly people, cerebral atrophy is common, and so subdural hematomas can follow relatively minor head injury. When the calvaria is struck, or strikes an immobile object or surface, the brain undergoes a swirling motion within the cranial cavity.¹⁰ This rotatory or spiraling movement over the internal bony ridges of the calvaria compresses and exerts shearing pressure on the brain and stretches blood vessels, resulting in hemorrhage and degeneration. Because of anatomical differences between the brain of humans (which has a diencephalic flexure) and that of domestic animals, rotational deformation may be less important in our patients.¹¹

The CNS parenchymal injuries can be described as **concussion**, **contusion**, and **laceration**. Concussion can be defined in several ways, one being the brief loss of consciousness that results from an abrupt head injury, which produces an episode of rapid acceleration/deceleration of the brain. Neuropathological evaluation of concussion is rarely possible, as the clinical deficit is usually temporary, but an axonal disturbance is suspected. Concussion is associated with a variety of permanent pathological changes if the inciting insult occurs repeatedly, as in the so-called sport of boxing: Characteristic of the brains of professional boxers is the formation of neurofibrillary tangles. Of course, comparable concussive injuries occur to the spinal cord as well as to the brain.

With a more violent force, the brain or spinal cord is contused; there is maintenance of structure but loss of vascular integrity, resulting in hemorrhage into the parenchyma and meninges in relation to the point of impact. Bony deformation or fracture of the calvaria result in focal lesions:

1. Direct (coup) contusions immediately below the impact site
2. Indirect (contrecoup) contusions to the brain at the opposite point of the skull.

If the head is mobile when the injury occurs, as is the norm, the contrecoup lesion can be larger than the coup lesion. Contrecoup hemorrhages result from tearing of leptomeningeal and parenchymal blood vessels; the calvaria and brain are brought into closer than normal apposition at the point of impact, and consequently meningocortical vessels are stretched and distorted at the contrecoup point. Microscopically, an area of contusion is sprinkled with perivascular hemorrhages, and there is degeneration of the neuroparenchyma. Small lesions scar over with astrocytes,



Fig. 4-1. **A**, Dorsal view of skull; nasal bones at bottom, sagittal crest at top. Bilateral fracture of frontal bone with fractured outer table of frontal sinus (F) reflected. **B**, The sectioned brain reveals extensive hemorrhage in the frontal lobe, basal nuclei, and brain stem.

whereas large foci liquefy and form cysts, marked by the presence at their margins of hemosiderin-laden macrophages that persist for weeks or months. Where parenchymal hemorrhages alone are encountered, the pathologist must consider in the differential diagnosis the possibilities of a coagulation disorder and vasculopathy, as well as trauma.

In humans, a diffuse pattern of parenchymal damage is recognized in association with very severe head trauma. These patients typically become unconscious from the moment of impact and remain comatose until death; if they survive, they are severely incapacitated (vegetative). Their injury is a **diffuse axonal injury**, thought to result from

acceleration/deceleration forces resulting in shearing strains that directly disrupt nerve fibers at the moment of impact^{10,12-14} or that impair axoplasmic transport, leading to focal swelling and subsequent segmentation of the axon.¹⁵ This diffuse axonal injury is believed to account for their comatose state and death. These patients less frequently have skull fractures or subdural hemorrhages. These diffuse lesions are seen grossly as small hemorrhages in central fiber tracts (corpus callosum, rostral brain stem) and microscopically appear as numerous focal axonal swellings. These have been produced in studies of head injury in the cat and primates but appear not to have been recognized in spontaneous trauma cases in animals.

Finally, most severe is laceration, wherein the CNS tissue is physically torn or disrupted by bony structures lining the cranium or by penetrating objects such as bone fragments. This is the most serious of the three categories, and also carries with it the risk of contaminating infection if the fracture is compound. The tendency for penetration by a foreign object depends on its size, the force, and the external cushioning layers (skin, haircoat, helmets for people). A small object (a bullet, head of a hammer) moving at high velocity is more likely to penetrate than a large object. Penetrating missiles produce track lesions and secondary, more widespread damage from the transitory displacement of the brain.¹⁶

Focal meningeal hemorrhage is a common sequel to severe head injury and may constitute a surgical emergency. In humans, epidural hematomas most commonly result from laceration of the middle meningeal artery, or vein, or both vessels¹⁷; less often, other vessels are the source of hemorrhage. An associated skull fracture is very common. Subdural hematomas usually follow disruption of bridging cerebral veins that drain into the dural venous sinuses. Subdural hematomas can follow a subacute to chronic course in humans, with repeated cycles of bleeding, clot organization, and fresh granulation. Subdural hematomas are seen in animals after automobile accidents or other severe forms of injury, but subarachnoid hemorrhage is more common. The importance of these hemorrhages is that they develop into space-occupying masses that indent and compress the underlying brain. Progressive enlargement of the hematoma can result in secondary effects: severe, widespread brain edema, areas of ischemia, herniations, midline shift, and lethal brain stem compression. "Duret" hemorrhages deep in the pons result from torsion of penetrating arteries as the brain stem is compressed and displaced ventrally. Subarachnoid hemorrhages usually occur only with significant parenchymal damage. In humans, vasospasm and fatal cerebral ischemia are recognized complications of subarachnoid hemorrhage.¹⁸ Oxyhemoglobin is believed to be the primary spasmogenic agent.

The injuries to the brain and spinal cord produced by trauma vary considerably, depending upon three factors: the



Fig. 4-2. Epiphyseal fracture in C2 vertebra (arrows) that resulted in myelomalacia, deer fawn.

severity, speed, and duration of the distortion. Acute, explosive injury, as with a sudden intervertebral disk prolapse, may produce hemorrhage, edema, and ischemia; gray matter is more sensitive to such injuries than is white matter. A displaced vertebral fracture (Figs. 4-2 and 4-3) carries the added risk of spinal cord laceration or even transection. The resulting clinical deficits are usually peracute in onset, painful, and dramatic. There is an extensive literature describing the clinical, pathological, and biochemical findings in spontaneous and experimental acute spinal cord injuries.¹⁹⁻²¹ The impetus for such studies is the unfortunate frequency with which these traumatically induced injuries occur in humans and animals. For example, of 211 vertebral column fractures in dogs and cats, 189 were the result of automobile accidents.²² Such vertebral fractures/dislocations do not occur randomly but are most common about the thoracolumbar junction, where the vertebral column is more mobile and less rigidly braced.

Studies by Griffiths²³ of traumatically induced spinal cord injuries in the dog and cat well highlight their complexity: Similar types of vertebral injuries can result in diverse patterns of spinal cord changes, whereas comparable types of spinal cord damage can have a variety of causes. If the spinal cord is acutely damaged, leukocytes (mainly neutrophils) enter the damaged tissue in response to chemotactic signals within 3 to 6 hours. Blood monocyte-derived mononuclear macrophages are evident by the third day, and the

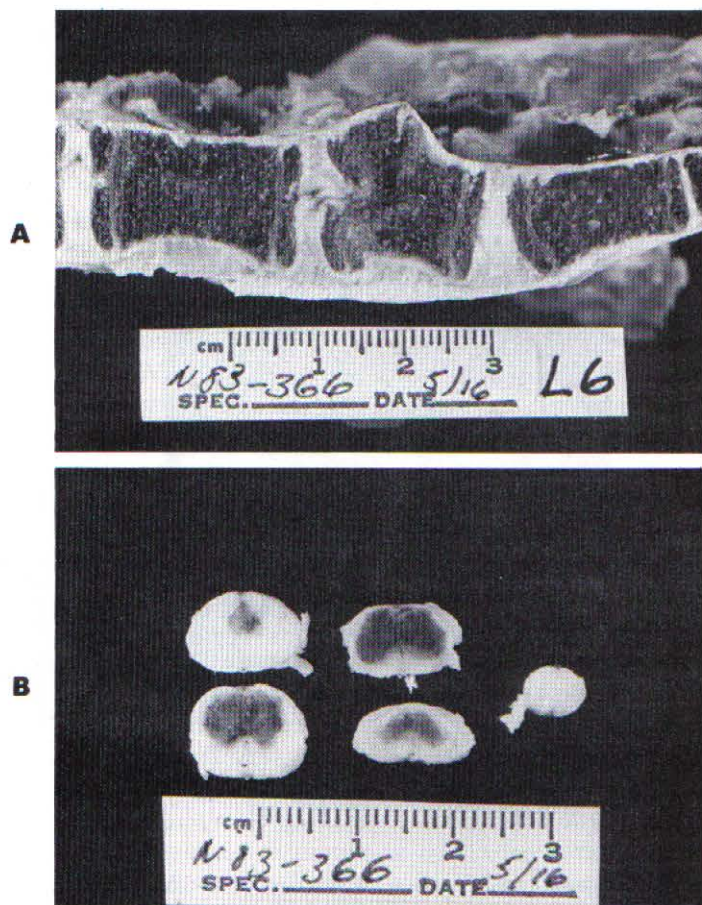


Fig. 4-3. A, L6 fracture/displacement in a lamb. B, Resulting spinal cord compression and central hemorrhagic necrosis.

neutrophilic influx wanes by day 5.^{24,25} Cell death in the gray matter may be evident by 4 hours, but the area of necrosis progressively expands for a few days.²⁶ In some cases, the whole spinal cord is necrotic, maintained in situ by a meningeal sleeve. The tissue liquefies, becoming soft and paste-like. Less dramatic lesions produce central cystic cavities. From the level of spinal cord injury, a core of necrosis may extend cranially and caudally, typically in the base of the dorsal funiculi.^{23,27} Isolated areas of necrotic tissue, removed from the immediate point of impact, probably reflect regions of ischemia following post-traumatic secondary injury to blood vessels.²⁶ Such areas of spinal cord necrosis are seen in cases of intervertebral disk prolapse, typically not at the site of spinal cord compression but in the adjacent one or two segments. Chromatolysis of ventral horn neurons occurs as a response to injury to proximal segments of their axons: the axonal reaction. Reactive astrocytes may contain immunoglobulins, apparently sequestered following blood-brain barrier disruption.²⁸

Acute, traumatic spinal cord injury is mediated by primary and secondary mechanisms.²⁶ The primary event is mechanical injury to the tissue, which may include compression, distraction, and laceration. Secondary changes are (in particular) the interruption to normal vascular perfusion, as well as such factors as electrolyte shifts, excitotoxic mechanisms of neuronal damage and free radicals. There is experimental evidence of very early axoplasmic and myelin changes, which may reflect calcium-mediated events, that precede vascular insufficiency.²⁹ Soon a whole cascade of further mediators of tissue degeneration appears on the scene: leukocyte products, prostaglandins, leukotrienes, free radicals, and excitotoxins.^{20,21} This has prompted the use of a variety of pharmacological antagonists in attempts to improve the management of acute spinal cord trauma.

Maximum preservation of spinal cord function is associated with slowly developing compressions, whether caused by a disk or by other extramedullary mass. Rapidly developing injuries, which result in extensive spinal cord necrosis, are probably deleterious by virtue of their effects on the vasculature.³⁰ There are local vascular effects (direct damage to small vessels, loss of autoregulation) and systemic circulatory changes (hypotension, diminished cardiac output). Acute spinal cord injury results in a significant reduction in spinal cord blood flow, which contributes to post-traumatic ischemia.²⁶

Sometimes spinal cord necrosis is encountered in the absence of obvious vertebral injury or spinal cord compression, requiring one to invoke concussive effects, vibratory forces, shock waves, or temporary deformation of the vertebral column (as in a whiplash injury) to account for its occurrence.

In contrast to acute injury, intermittent or slowly progressive compression of the CNS presents quite differently. Examples include the caudal cervical vertebral malformation-malarticulation syndrome in dogs, commonly seen in the Doberman Pinscher, and an expanding intracranial tapeworm cyst (a condition known in sheep as gid). Clinically, such disorders are marked by a chronic course of slowly worsening neurological deficits, sometimes punctuated by periods of clinical stability. These injuries do not produce acute hemorrhage and necrosis in the neural parenchyma. There may be a loss of motor neurons in the spinal cord ventral gray column of the Doberman Pinscher due to intermittent episodes of ischemia. However, such slow spinal cord compression characteristically results in loss of axons and their myelin sheaths in all funiculi with an attending fibrous astrocytosis. Fiber loss results in shrinkage of the spinal cord and is marked clinically by pronounced spastic paresis and proprioceptive deficits. In addition, there may be demyelination without axonal loss at the site of compression. Fish and Blakemore³¹ found that gradual compression of the growing spinal cord produced partial demyelination of axons in white matter funiculi. Thus, whereas vessels in the central gray matter of the spinal cord seem most sensitive

to the effects of acute trauma, slow spinal cord compression is largely expressed as a disorder of myelinated axons.

Brain injury from a slowly expanding mass, which may be intramedullary or extramedullary, is seen as atrophy of the compressed area of the brain. As the pyramidal system is constituted by single neurons and their long axonal projections, a focal injury to this tract can produce Wallerian degeneration over a considerable distance; for example, a sizable lesion within the internal capsule could also result in ipsilateral atrophy of the pyramid, reflecting corticospinal tract injury. In transynaptic degeneration, in contrast, a successive chain of interconnected neurons degenerates following a proximal injury. This occurs, for example, in the optic system.³²

In humans, there are various known or suspected sequelae to brain injury. Post-traumatic seizures is one outcome, thought to be due to the formation of epileptogenic scar tissue or to blood breakdown products.³³ A number of neurodegenerative diseases are thought sometimes to follow trauma, such as Parkinson's disease and the various forms of dementia that are seen in boxers.

References are on page 205.

VERTEBRAL MALFORMATIONS AND SPINAL CORD INJURY

A primary abnormality of vertebral body development can result in temporary or progressive spinal cord injury, leading to paresis and ataxia. Consistent with a developmental disorder, these clinical signs are usually seen within the first 1 to 3 years of life, although important exceptions occur. The site and the nature of the skeletal malformations vary, whereas the resultant myelopathy is fairly stereotyped. In some animals, notably the horse and the dog, this syndrome (affecting the cervical vertebrae) is a common cause of neurological disease. Cervical vertebral malformations occur sporadically in other animals, as do anomalies of thoracic, lumbar, sacral, and caudal vertebrae. Some of these disorders are associated with particular breeds of animals and may be inherited. Vertebral malformations in domestic animals have been reviewed by Noden and de Lahunta.¹

The clinical signs reflect the location of the compromised spinal cord segments. As a rule, thoracolumbar malformations cause a progressive symmetrical spinal cord myelopathy with spastic paraparesis and ataxia of the pelvic limbs. Cervical vertebral malformations are associated with neurological signs that can be slowly progressive or sudden in onset, followed by a varying degree of progression. These often produce pelvic limb signs that are more obvious than the forelimb deficits. One explanation is that the compressive lesion interferes more with the superficial pathways in the lateral funiculi, which are predominantly pelvic limb proprioceptive tracts. This results in the more apparent pelvic limb ataxia. This may be augmented by the further

distance of the pelvic limbs from the center of gravity of the animal.

Horse

In years past, paresis and ataxia in the horse has often been referred to as wobbler disease. The term wobbler has sometimes been used synonymously with the paresis and ataxia that results specifically from the injury caused by cervical vertebral malformation. However, it has also been used to describe a clinical syndrome without specifying the nature of the underlying process affecting the spinal cord (inflammation, infarction, trauma), and so the demise of this term would seem for the best. In **cervical stenotic myelopathy (CSM)**, stenosis of the vertebral canal results from malformation and/or malarticulation of cervical vertebrae. Malformation results in stenosis of the vertebral foramen through which the spinal cord passes, and so the spinal cord is compressed. Vertebral instability or malarticulation leads to stretching and/or compression of the spinal cord if the vertebrae become malaligned, which occurs when the neck is flexed. The common and major cause of paresis and ataxia in young horses was assumed to be CSM until careful studies identified a second and distinct disorder—equine degenerative myeloencephalopathy (EDM)—which clinically can be confused with CSM. In EDM, there is no underlying vertebral disorder, and the fundamental process is not spinal cord trauma but an intrinsic, diffuse spinal cord degeneration. It is discussed in Chapter 5.

Cervical stenotic myelopathy occurs in all the major horse breeds. Its development is not random, however, as rapidly growing animals (large for their age) are at an increased risk.² There is a marked sex difference, males being more commonly affected than females.^{3,4} These risk factors for the development of CSM may be linked insofar as growth rate and body size, although dependent upon the nutritional regimen, are greater in stallions than in mares. Clinical presentation is most common between 6 and 12 months of age, usually within the first 3 years of life, but sporadic cases at 4 years of age and older have been recorded.⁴⁻⁶ In the more slowly growing warmblood breed, CSM is commonly encountered at 5 to 7 years of age.⁷ The development of spinal cord compromise probably evolves insidiously with intermittent progression, but owners often observe and report an abrupt onset of neurological deficits. Sometimes this is said to follow a fall, although it is likely that the fall resulted from an unappreciated but already present spinal cord compromise. The classical clinical features are symmetrical spastic paresis and ataxia of all limbs, pelvic limbs worse than thoracic. These signs reflect the underlying white matter damage and so are of upper motor neuron (UMN) and general proprioceptive (GP) type. In the thoracic limbs, this produces a "floating" gait in which the advancing limb over-reaches before being placed to the ground. There is also spasticity of the pelvic limbs, but the general proprioceptive deficit is usually more flagrant, particularly if the



Fig. 4-4. Cervical stenotic myelopathy, horse. The caudal aspect of the foramen of the C5 vertebra is normal. In contrast, the foramen at C6 is narrowed from proliferation of the articular processes.

horse is circled. With circling, the limbs are excessively abducted and crossed, and sometimes the animal pivots on a limb as it cannot coordinate the rapid and precise movements required to accommodate tight circling. At a normal walk, the hind quarters sway laterally, and the animal may scuff the hooves. Rarely there is appreciable asymmetry of spinal cord signs; when present, it usually results from compression of the spinal cord by an enlarged (and degenerate) articular process. Progression proceeds at a very variable rate, and horses affected for weeks or months may be static at presentation but are euthanized because they are unsafe to ride or even handle.

The clinical diagnosis of CSM depends upon the historical data, signalment, observations at neurological examination, and radiographic procedures with the neck in neutral, extended, and flexed positions. The pathological basis for spinal cord injury includes a number of vertebral hard and soft tissue changes. In most cases of CSM, more than one pathological change is present, and spinal cord injury probably results from the combined effects of the abnormalities. For example, a combination of mild vertebral foramen stenosis with some degree of vertebral malarticulation is prob-

ably common. Equally important, however, is recognizing that pathological changes may be discovered that make no contribution to the clinical deficits. For example, some degree of osteoarthropathy of articular processes may be observed radiographically that does not contribute to the spinal cord insult. This can be determined by myelography. The range of pathological alterations in CSM are as follows:

1. Malformation of the vertebra with stenosis of the vertebral foramen
2. Malarticulation of cervical vertebrae, also described as malalignment, instability, or subluxation
3. Degenerative osteoarthropathy of intervertebral articular processes with osteophyte formation (Fig. 4-4)
4. Enlargement of the vertebral dorsal lamina and ligamentum flavum,⁴ which compromises (depresses) the spinal cord upon hyperextension of the neck
5. Formation of synovial cysts (Fig. 4-5), which usually is seen in association with static stenosis⁴ and can produce considerable compression

Whitwell⁸ has listed further changes. Failure of vertebral body modeling with dorsoventral narrowing of the foramen seems to be the most frequently recognized basis for CSM.

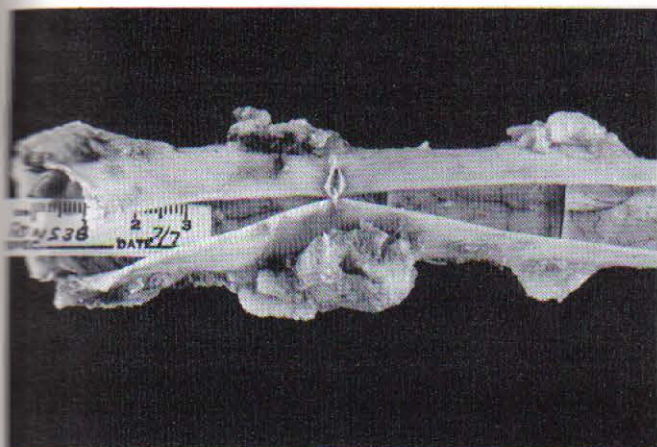


Fig. 4-5. Cervical stenotic myelopathy, horse. Thick-walled extradural synovial cyst at C7.

The cranial end of one vertebral foramen and the caudal end of the other foramen of the adjacent vertebra are usually involved. Involvement of the cranial and caudal aspects of a single vertebral body is uncommon.

Detection of abnormalities in plain lateral radiographs of the cervical vertebrae have been facilitated by the studies of Mayhew and colleagues,⁹ who plotted, between the second and seventh cervical vertebrae, the minimum sagittal diameter (MSD) and minimum flexion diameter (MFD) for horses either above or below 320-kg body weight. In horses with **static stenosis** (see later in this section), the MSD is focally or multifocally diminished, regardless of the position of the neck. In horses with **dynamic stenosis**, MSD is adequate in any position of the neck, but the MFD is subnormal upon flexion of the neck. Sometimes such measurements reveal abnormalities at two or three joints. Perhaps the most frequent site of stenosis and spinal cord injury is at C3-C4, but other joints, especially C4-C5, C5-C6, and C6-C7 are common locations.^{3,10} Radiologically, degenerative joint disease of the articular processes is seen as enlargement of the articulation, increased periarticular bone density, and loss of definition of the articular space. In vertebral malarticulation or instability, the cranial aspect of the vertebral body angles up, narrowing the vertebral canal when the neck is flexed.

If surgical treatment is under consideration,¹¹ then a myelographic procedure is also justified. Surgical stabilization is most reasonably attempted in those cases in which the pathological disorder is not a constant (static) spinal cord compression but rather is a fluctuating (dynamic) insult, produced by flexion of the neck; this is the form that has been described as cervical vertebral malarticulation or instability.

The results of cerebrospinal fluid examination in CSM may be normal or may show a mild xanthochromia and/or an elevation of the protein level.⁹ Examination of CSF is

also an important tool in eliminating other differential diagnoses: Pleocytosis occurs more commonly in protozoal and viral infections, and marked xanthochromia in equine herpes 1 myelopathy. Examination of CSF does not distinguish between CSM and EDM.

Observations made at necropsy of horses with CSM depend in part on how the cervical vertebrae are examined. For complete evaluation, disarticulation and examination of each intact vertebra is the most satisfactory. In the course of a busy afternoon's necropsy service, it is sometimes necessary to employ less than optimal techniques. Careful sectioning of the cervical vertebrae in a parasagittal plane with a band saw provides the spinal cord intact if the operator is experienced. This approach does also leave the cervical vertebral column united, and it can be aligned in neutral, extended, and flexed positions to examine for evidence of malarticulation and compression. The band saw destroys half of each vertebra and may well puncture and collapse epidural synovial cysts, which are sometimes present in this disorder.

If the cervical vertebrae are individually disarticulated, dorsoventral narrowing of the vertebral orifices can clearly be seen. Median section of such a vertebra reveals a funnel shape to the vertebral canal,⁹ narrowing toward the stenotic foramen. This preferred technique also permits a complete evaluation of both articular processes for evidence of degenerative changes, which are seen as mild to severe cartilage loss (fibrillation, pitting, eburnation), and reactive osteophyte formation, which can markedly enlarge and distort the process. The associated joint capsules are often markedly thickened. Expansion of the process in a medial-ventral plane can encroach upon and injure the spinal cord. The vertebrae should be examined for thickening of the ligamentum flavum.

At points of compression, the spinal cord is often appreciably flattened, especially when compared to adjacent unaffected segments. It is also firm if there is astrocytic sclerosis. In a minority of cases (perhaps 20%),^{5,12} compression occurs at more than one cervical intervertebral joint.

Microscopically, changes depend on the duration and severity of the injury (Fig. 4-6). Where the spinal cord is impacted, degenerative changes are found in the white matter in all funiculi without selective involvement of any tracts. Myelin sheaths are ballooned, and axons are lacking or may be swollen and grayish or eosinophilic. Ballooned myelin sheaths may contain macrophages, which typically have small, hyperchromatic nuclei. Transverse sections of the spinal cord allow an evaluation of the distribution and severity of myelin injury. Longitudinal sections are equally as important (both should always be taken in the histological examination of any spinal cord), as they reveal the typical chains of digestion chambers and so can allow differentiation of pathological from artifactual white matter changes.

In chronically compressed spinal cords, evidence of active myelin degeneration is less prominent, whereas a dis-

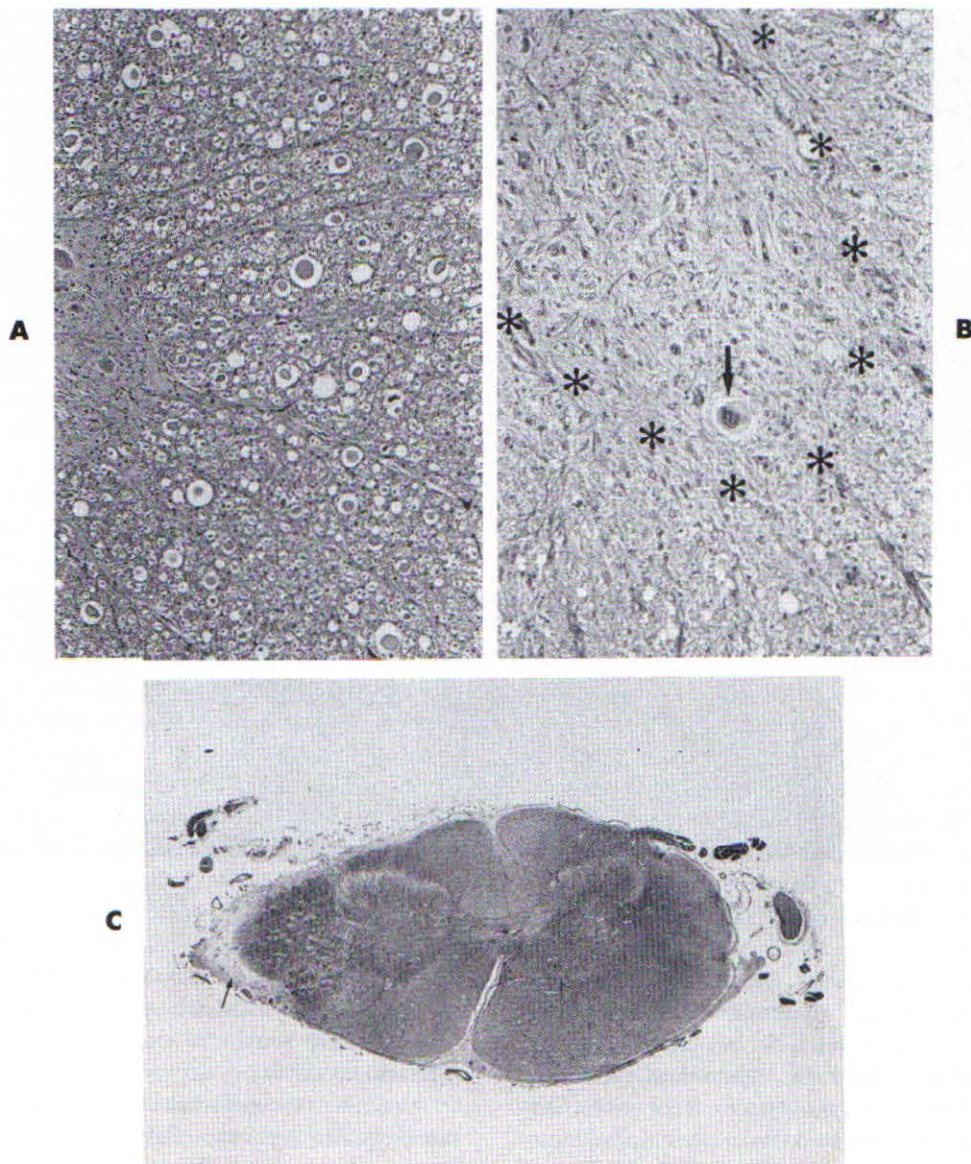


Fig. 4-6. Spinal cord compression. **A**, Spheroids in ventral funiculus, deer. (H&E, $\times 35$.) **B**, Chronic compression has resulted in motor neuron loss and pronounced astrocytosis, ventral horn (outlined by asterisks). A single degenerate neuron remains (arrow). Dog. (H&E, $\times 140$.) **C**, Asymmetrical compression of the cervical spinal cord, calf. Note the markedly thickened leptomeninges (arrow). (Masson's trichrome, $\times 8$.)

secting interstitial astrocytosis is progressively more conspicuous. White matter and, to a lesser degree, gray matter are affected.¹³ In chronic compressive myelopathies, perivascular fibrosis is also present. Loss of motor neurons may be evident with small microglial stars and gemistocytic astrocytes in their stead. Neuron loss causes Wallerian degeneration in the ventral rootlets. Motor neuron loss may reflect episodes of ischemia (to which these cells are particularly sensitive) from stretching of the spinal cord over the lip of a malaligned vertebral body.

At spinal cord sites cranial and caudal to the primary

injury, Wallerian degeneration is found in *either* the ascending or descending pathways, respectively (Fig. 4-7). Cranial to the site, this degeneration is predominantly in the dorsal funiculi and in the spinocerebellar tracts on the surface of the lateral funiculi. In contrast, Wallerian degeneration in descending tracts caudal to the site is anticipated deep in the lateral funiculi and in the ventral funiculi, adjacent to the median sulcus and below the pia. This is an important principle to grasp, for it permits the histopathological recognition of a myelopathy consistent with a focal injury, whether from CSM, intervertebral disk prolapse,

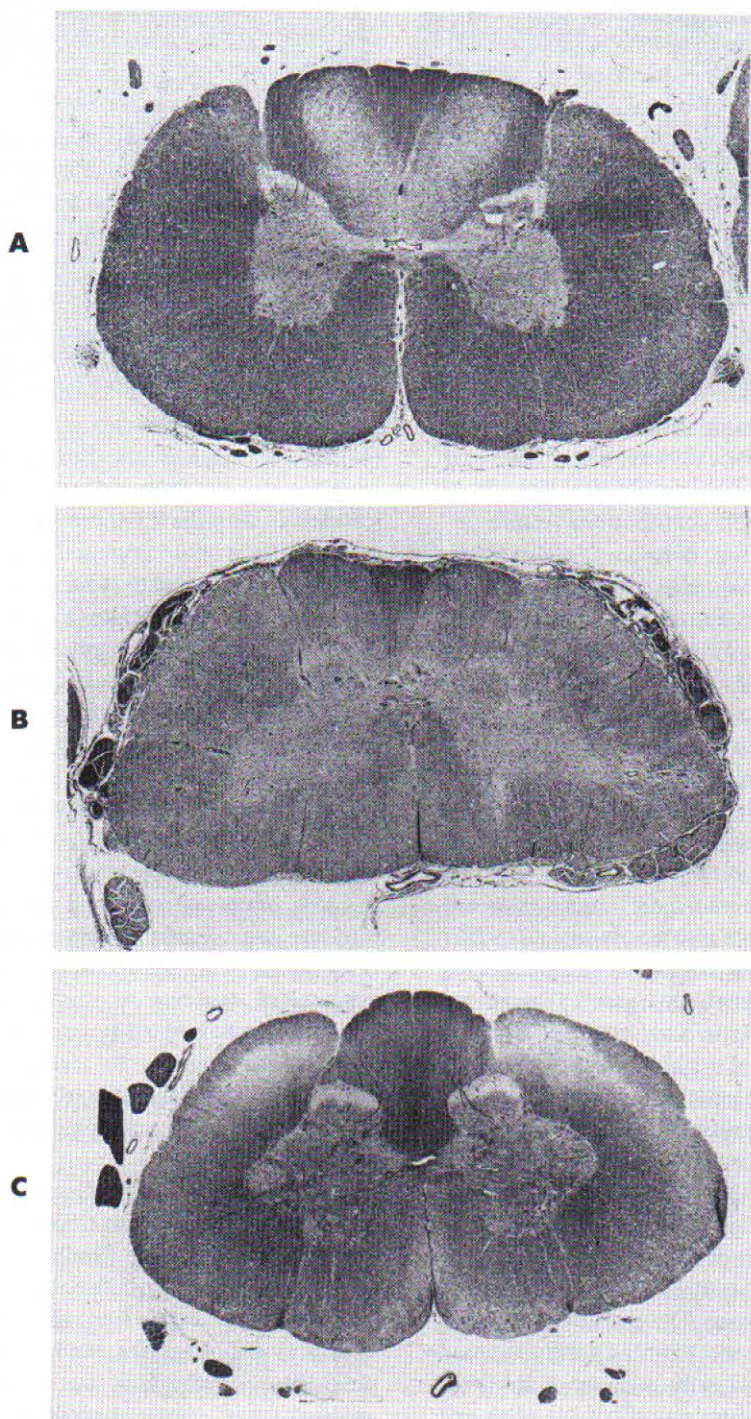


Fig. 4-7. Chronic spinal cord compression. **A**, Cranial to the compression, degeneration is seen in the dorsal columns and faintly in the spinocerebellar tracts. (Luxol fast blue, cresyl echt violet, $\times 11$.) **B**, At the point of compression, the spinal cord is slightly narrowed in the dorsoventral plane. All funiculi are degenerate and somewhat pale; compare with normal myelin staining in the spinal roots. (LFBCEV, $\times 13$.) **C**, From a different dog, spinal cord below a focal compression shows degeneration in the lateral corticospinal tracts and ventral funiculi. (LFBCEV, $\times 13$.)

vertebral fracture, or whatever. Should there be two points of spinal cord compression, then the segments *between them* have degeneration in both ascending and descending pathways. It is important to remember that the degree of Wallerian degeneration observed is dependent on the amount of axonal destruction at the site of the compression. Loss of myelin without axonal disruption at the site of the injury will not initiate this process.

Ultrastructural examination of horses with signs of CSM for 4 to 24 months revealed a mixture of Wallerian degeneration and primary demyelination with remyelination at the sites of injury.¹⁴ Astrocytic gliosis was conspicuous, and occasional spheroids were noted.

Microscopic studies of affected bones reveals osteochondrotic changes with retention of cartilage cores in trabecular bone and osteopetrosis or subchondral cysts.^{4,9,10} These changes reflect a generalized skeletal disturbance and are not limited to the vertebrae.^{3,15} This osseous disorder is thought to be multifactorial, with contributions from a genetic predisposition, overnutrition, hormones, and perhaps other factors. Some horses have enlargement of the ligamentum flavum, which is from fibrovascular and fibrocartilaginous tissue proliferation. This will blend with a fibrotic, thickened joint capsule.⁴

Epidural **synovial cysts** have sporadically been recorded in horses with CSM.^{7,8,16,17} They are about 1 to 2 cm in diameter and project into the vertebral canal from a dorsal or dorsolateral position, may be multiple, and may cause considerable compression.¹⁰ They appear to be the result of an arthropathy with the formation of an abnormal synovial joint with which they may communicate.⁸ These cysts are most common at C6-C7 but have also been seen at C5-C6.

Occipitoatlantoaxial malformation (OAAM) occurs with some frequency in the **Arabian horse**¹⁸⁻²⁰ as an autosomal recessive trait and rarely in other breeds.²¹ Affected foals are typically tetraparetic at birth, although some malformations are milder, allowing for normal early development with spinal cord compromise occurring postnatally. Some degree of anomalous development may go unsuspected throughout the life of the Arabian.¹⁸ A number of patterns of OAAM malformation are recognized. The important changes are partial or complete fusion of the atlas to the occipital bones with the development of occipital condylelike structures on the atlas. The dens is hypoplastic and luxates beneath the atlas, and the axis develops broad transverse processes while those on the atlas are diminished. Thus there is said to be "occipitalization" of the atlas and "atlantalization" of the axis. Clinically, the head posture is abnormally extended, and normal atlanto-occipital mobility is lost. The abnormalities described can be palpated and confirmed radiographically. The CNS is injured anywhere from the caudal medulla to the level of the luxated dens. Comparable malformations have only rarely been described in other domestic animals,¹⁸ including calves^{22,23} and cats,²⁴ and may be associated with atlantoaxial subluxation.

Dog

A syndrome, varying from having an acute onset to chronic, slowly progressive cervical spinal cord compression, occurs in the dog that is similar to that just described in the horse (CSM). This canine disorder has been recognized in certain larger breeds for decades and is described in an extensive literature under a variety of designations. Because of the prominent ataxia, these dogs have also been called wobblers. Other terms employed are vertebral instability, vertebral subluxation, cervical spondylopathy, cervical spondylomyelopathy, cervical spondylolysis, and the term we prefer, **cervical vertebral malformation-malarticulation**. The disorder is most common in the **Doberman Pinscher** and **Great Dane** breeds²⁵⁻²⁹ and has been recorded sporadically in other large breeds.^{30,31} General experience is that males are more commonly affected than females, although in the Borzoi dog all affected animals were females.³² Affected dogs present because of neurological deficits anywhere between 1 and 11 years of age. Early presentation is more common in the Great Dane, whereas Dobermans are typically seen at about 6 to 8 years of age.³³ The owners' concern relates to a pelvic limb ataxia, usually of insidious onset and progressive for months. Affected dogs stand base wide in the pelvic limbs, and, when walking, show spastic paresis and ataxia, with hypermetria especially evident on the turn. They drag the toes, resulting in wearing of the nails, and may stand knuckled over. The forelimb gait is quite different. Usually there is a slight delay in the onset of protraction, followed by a mild over-reaching or floating with a hyperextended (spastic) limb. Occasionally the paw drags on its dorsal surface. In a few dogs, the forelimb gait consists of very short, choppy, stilted strides. Because the injury occurs caudally in the cervical vertebrae, evidence of denervation atrophy of the supraspinatus and infraspinatus muscles may be seen, with prominence of the spine of the scapula. In severe cases, affected dogs are nonambulatory. Some affected dogs are resistant to manipulation of the neck, and some present with a complaint of overt neck pain.

A presumptive clinical diagnosis can be substantiated by ancillary procedures. The CSF is often normal or shows an elevated level of protein. Radiographic studies are definitive (Fig. 4-8), including both lateral and dorsoventral views. This syndrome results from the summation of a number of structural abnormalities, and many can be identified in plain films. Myelograms are important to substantiate the areas of spinal cord compression, their severity, and their likely cause (vertebra, ligament, disk). Myelography is justified if surgical intervention is under consideration or to definitively rule out other considerations, such as neoplasia. Caudal cervical vertebral malformation-malarticulation (CVMM) most commonly affects the C6-C7 intervertebral joint and, in some dogs, other joints also (usually C5-C6).³⁴ Because a number of pathological changes are found at surgery or necropsy, it is a moot point which is the primary

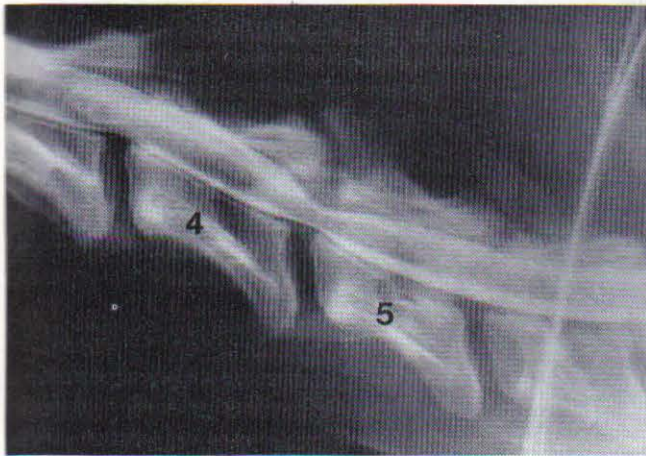


Fig. 4-8. Cervical vertebral malformation-malarticulation, dog. Myelogram shows narrowing of the vertebral canal between C4 and C5.

derangement and which changes are secondary. One interpretation is that there is an underlying vertebral malformation, of variable degree. Because of this malformation, the vertebra does not articulate normally with its neighbors at the synovial joints (articular processes) and at the synchondrosis (the intervertebral disk). Presumably, the caudal cervical vertebrae bear much of the strain involved in supporting the head and the neck. An aberrant vertebra puts undue stress on its associated joints and ligaments. Hence it is argued (by some) that these soft tissue changes, which contribute significantly to inducing the spinal cord compression, are a secondary development—a degenerative osteoarthropathy due to chronic malarticulation. However, this scenario is not universally accepted, and other interpretations have been offered.³² The pathological changes found in dogs with CVMM follow.

1. Two forms of vertebral malformation are recognized. Stenosis of the foramen results in static compression of the spinal cord. Abnormality in the shape of the vertebral body results in instability and "tipping" of the cranial edge into the vertebral canal, especially upon flexion of the neck. This change, from a normally rectangular to a rhomboidal shape, may relate to abnormalities in closure of vertebral body epiphyses,³³ which results in an enlarged caudal vertebral end plate. This is more common in younger dogs.
2. Thickening of the dorsal aspect of the annulus fibrosus (Fig. 4-9) elevates the dorsal longitudinal ligament on the floor of the vertebral canal and compresses the spinal cord. This is a common contributor to the Doberman Pinscher disease,³⁵ especially in the older dogs. Fibrous thickening of the dorsal annulus is thought to result from abnormal mechanical forces exerted on the intervertebral joint secondary to malformation, malarticulation, and/or laxity. The disk

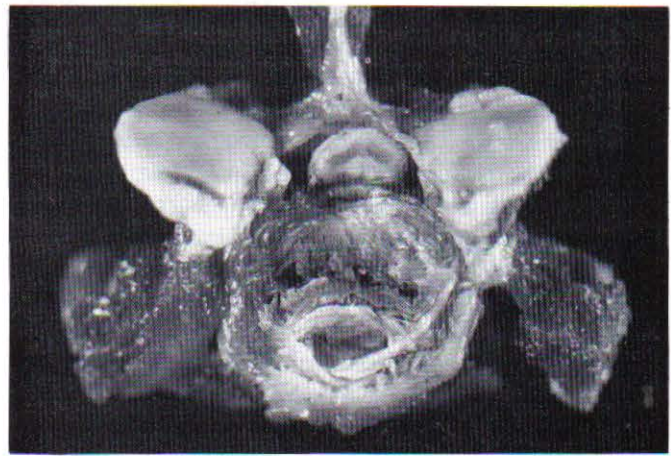


Fig. 4-9. Cervical vertebral malformation-malarticulation, dog. At cranial C7, massive proliferation of the degenerate disk narrows the vertebral foramen.

space is often narrowed ventrally, but rupture of the annulus with protrusion of the nucleus pulposus into the vertebral canal occurs in only a minority of cases. Sometimes calcified material is detected radiographically within the disk space. Narrowing of the disk space causes the proliferated annulus and associated dorsal longitudinal ligament to bulge into the vertebral canal. This can be shown myelographically, and the bulge removed by stretching out the neck. Spondylosis may be found in vertebrae at points of joint instability.

3. Hypertrophy of the ligamentum flavum and sometimes the joint capsule of the articular processes impinges on the spinal cord from a dorsal or dorsolateral direction.
4. Proliferative changes resulting from osteoarthrosis of the articular processes or thickening of the vertebral dorsal lamina may result in spinal cord injury.

At necropsy, the spinal cord may be visibly compressed and firm. Lesions are usually found in the sixth and seventh cervical spinal cord segments. Microscopically, the changes found are as for those detailed earlier in equine CSM. Chronic insults commonly deplete both white and gray matter; the latter is seen as ventral horn neuronal loss, replacement of cell bodies by gemistocytes, and Wallerian degeneration in the segmental ventral roots that supply the muscles of the scapula. Wallerian degeneration is found above and below the site of impact in the ascending and descending tracts, respectively. The thickened, hypertrophic annulus consists of abundant fibers of fibrocartilaginous tissue.

The cause is as well or as poorly understood as for equine CSM. A breed association is more clearly established, and an hereditary basis is established for the Borzoi and proposed for the Great Dane and Doberman Pinscher. Overnutrition and excess dietary calcium in the early months of life are

felt to be contributory to poor modeling of the growing skeleton. Animals with a severe vertebral malformation developing in early life constitute the population presenting as young dogs. Those with a milder bony disorder, in which spinal cord compression results from acquired degenerative joint changes, may not be seen until later life.

In two young Rottweiler dogs (15 and 18 months), cervical spinal cord compression due to thickening of the ligamentum flavum in the absence of other vertebral changes has been observed.³⁶ In these dogs, the site of the compression was at C2-C3.

A number of reports have described young dogs with signs of progressive spinal cord injury resulting from deformities of individual vertebral bodies. The abnormally developed vertebral bodies are often said to be **hemivertebrae**, but this is an oversimplification for a complex vertebral malformation. Many cases occur in small, brachycephalic breeds, particularly the **Pug**, **Pekingese**, and **English** and **French Bulldogs**. Many of these dogs have corkscrew tails, which is due to caudal vertebral malformation. Done and colleagues described their experience with 20 cases, of which 7 were Pug dogs.³⁷ Most (15 of 20) presented at or before 1 year of age, but some not until 6 years. Concerns of their owners related to pelvic limb dysfunction, which sometimes was unilateral. Some dogs were incontinent of urine, feces, or both. The sex distribution was approximately equal. Vertebral scoliosis and/or kyphosis could be seen and palpated. Radiographic abnormalities extended between T2 and L1 and occasionally affected more than one vertebra. Malformations were most common at T7-T9 and the abnormal vertebrae were wedge-shaped. Kyphosis was sometimes severe, resulting in misshapen dorsal spinous processes to accommodate the abnormal conformation. Inevitably, dorsal displacement of the offending vertebra had resulted in spinal cord compression. Some affected dogs had other skeletal disorders such as hip dysplasia, and concurrent malformations of the mandible and patella have also been noted.³⁸ Thoracic hemivertebra has been observed in the **German Shorthaired pointer** and an autosomal recessive basis for the disorder established.³⁹ In all four dogs reported, an abnormality at T4 was common and spinal cord injury occurred between T3 and T5. In these animals, difficulty in gait was noted by 6 weeks of age and within a week had progressed to paraplegia. Leyland⁴⁰ has reported a severely paretic and ataxic female 17-week-old **Doberman Pinscher** puppy with a T5 hemivertebra; doubtless many other sporadic cases have been reported. It must also be remembered that vertebral malformations may be detected radiographically as an incidental finding, for example, in the caudal thoracic spine in English bulldogs,³⁸ and their presence may be unrelated to the neurological disorder.⁴¹ This midthoracic vertebral malformation can also occur sporadically in any breed. As a rule, the signs of progressive spastic paraparesis and ataxia occur after a few months of age and before 1 year. This



Fig. 4-10. Vertebral malformation, dog. The vertebral foramen in C2 funnels from cranial to caudal. The cranial orifice of C3 is also stenotic. Basset pup.

appears to relate to the increasing severity of the kyphosis as the dog grows.

Progressive pelvic limb dysfunction from 8 weeks of age, which progressed to severe paraparesis by 14 weeks, was recorded in a **Basset hound**.⁴² Vertebral malformation with stenosis of the vertebral canal occurred at the thoracolumbar junction (T12-L1). Histopathological examination revealed degeneration of central gray matter and the white matter funiculi of the compressed spinal cord. We have seen three female Basset hounds with slowly progressive spastic paraparesis and ataxia of the pelvic limbs starting between 8 and 12 weeks of age. Myelography showed a stenosis of one vertebra between T10 and T13. One was confirmed at autopsy by an associated compressive myelopathy. The other two slowly improved and presumably grew out of their problem. An earlier report⁴³ described a syndrome of paraparesis, progressing to tetraplegia in some cases, in male Basset hounds. The onset was by 6 months of age, and some pups were affected from birth; the extent of the progression was variable. The disorder resulted from a deformation of the third cervical vertebra with spinal cord compression at the C2-C3 or C3-C4 articulation. We have seen a single Basset hound with stenosis of multiple cervical vertebrae (Fig. 4-10).

On rare occasions, an abnormally developed vertebral body and a spinal cord anomaly are encountered concurrently. This is not surprising, as the development of the spinal cord and vertebral column is dependent on the interaction between the notochord, neural plate, and mesodermal sclerotomes. First, the possibility must be considered that a primary vertebral malformation has simply injured a normally developing spinal cord, resulting in disorganization and scarring from early life. In other circumstances, however, anomalies in one system seem to induce abnormal development in the other. It is common

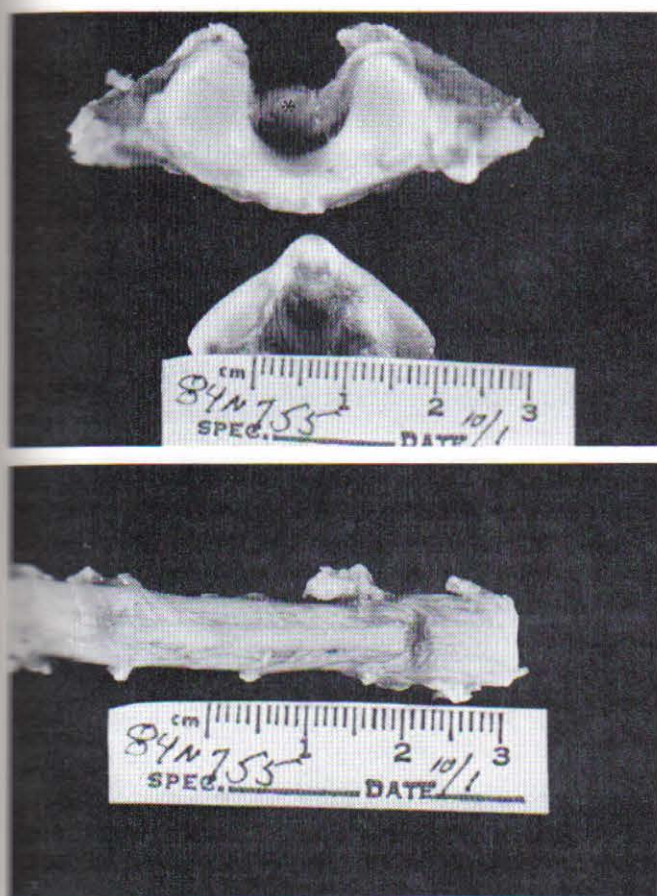


Fig. 4-11. Cervical vertebral malformation, dog. **A**, Laminectomy at C1 reveals how the transverse ligament of the atlas (*asterisk*) has been pushed into a vertical plane. Below is the hypoplastic dens. **B**, Subluxation of the axis causes a dorsal displacement of the spinal cord. This results in indentation in the spinal cord caused by the caudal edge of the arch of the atlas.

to see varying vertebral malformations with several forms of myelodysplasia.

More unusual are other associations, such as the duplication of the colon in a 9-week-old Labrador Retriever pup with vertebral deformity at T4 and T5.⁴⁴ Comparable concurrent anomalies have been recognized in humans.

Atlantoaxial subluxation (Fig. 4-11) occurs in puppies and young adults of the toy breeds of dogs such as the **Yorkshire Terrier, Chihuahua, Pomeranian, and Miniature Poodle.**⁴⁵⁻⁴⁷ The disorder is associated with a small or nonexistent dens. It is often presumed that this is due to developmental failure, but degeneration of the dens, similar to the femoral head degeneration in these toy breeds of dogs, is also a consideration. Clinical signs, which can vary from neck pain to tetraplegia, result from dorsal displacement of the axis with severe-acute or chronic-progressive spinal cord compression. Atlantoaxial luxation is recorded in the cat.⁴⁸

Other species

In 1985, a disorder manifest as congenital paraplegia was encountered in newborn **calves** in western Canada.⁴⁹ Most calves were of mixed beef breeds, and both sexes were affected. These calves were unable to stand or could stand only with assistance. They had a variety of skeletal abnormalities, including shortened, rotated, and curved limbs, enlarged joints, and a domed skull. Postmortem examinations revealed multifocal vertebral body malformations in the cranial thoracic to midlumbar regions. Enlarged and flared epiphyses of the vertebral bodies and expansion of articular processes produced a stenosis of the vertebral canal and severe spinal cord compression. Systematic studies of the skeleton revealed a widespread disorder, characterized by irregular contour and focal closure of metaphyseal growth plates with deformity of epiphyses and articular surfaces. Long bones in thoracic and pelvic limbs were affected. Of 19 calves examined at necropsy, 9 had a malformation of the cranial base, and 7 of the 9 were hydrocephalic. The episode affected progeny of cattle on four farms with a morbidity of 7% to 96%. Affected calves had low liver manganese levels, but it was unclear whether this was of primary importance. A genetic basis was considered to be unlikely. Investigations of subsequent episodes of this syndrome revealed an association with the feeding of moldy cereal straw to beef cows during pregnancy.⁵⁰ A fungal mycotoxicosis is considered a likely cause.

Few developmental vertebral abnormalities have been recorded in **sheep**. Of three rams that developed paralysis, one was available for clinical and pathological examinations.⁵¹ Ram lambs were being prepared for show and sale purposes and were fed a diet high in protein and energy, plus mineral supplementation. The animal studied, a 10.5-month-old Suffolk, was tetraplegic and initially could stand only with assistance. Plain radiographs revealed a misshapen third cervical vertebra. With time, this animal's neurological deficit improved markedly. At autopsy, sagittal section of the cervical spine revealed narrowing of the vertebral canal at C3-C4 and C4-C5. The third vertebral body was wedge-shaped, and microscopic examination revealed osteosclerosis of C2 and C3, as has been reported in equine CSM. The most severe spinal cord injury was found at the atlanto-occipital junction and C1-C2, and this was hypothesized to result from injury incurred from head butting. Probably the other two affected rams were similarly affected as a consequence of their "overnutrition." Although a tetraparetic lamb had both a hypoplastic dens and a malformed C5 vertebra, spinal cord compression was related to the latter defect.⁵²

Hemivertebra has been recorded in the **goat**⁵³ and occurs with some frequency in **mink**,⁵⁴ such that they were proffered for study as of possible comparative pathology value.

Miscellaneous cases

Multiple cartilaginous exostosis is a disorder of skeletal development that has been recognized in a number of animal

species.⁵⁵ Nodules of cartilaginous tissue, with a variable bony component, arise in the area of growth plates. Single cases are often designated osteochondromas, and malignant transformation can occur.⁵⁶ Vertebral involvement may produce spinal cord compression and paraparesis in young animals.⁵⁶⁻⁵⁸ Paraparesis has been observed in young adult cats as a result of spinal cord compression by extramedullary masses of vascular tissue. The primary lesion involves one or two thoracic vertebrae and extends into the vertebral canal.⁵⁹ The vasoformative tissue is thought to be malformative. Paraplegia has been associated with spinal cord compression from subperiosteal vertebral hemorrhage in the dog.⁶⁰ In such cases, a primary or acquired coagulation disorder should be considered.

References are on page 206.

INTERVERTEBRAL DISK DISEASE AND SPINAL CORD INJURY

Degeneration and protrusion of intervertebral disks is one of the most common causes of neurological disease in man and his best friend.¹ Certain breeds of dogs are particularly prone to develop this disease, most notably the Dachshund.² In contrast to the dog, myelopathy resulting from disk protrusion is decidedly uncommon in the other domestic animal species. Why this is so in the cat is unclear. A few cases of cervical disk protrusion are reported in the horse. In those animals that are of economic importance, their life span may be abbreviated before significant age-related disk degeneration can occur. Other neurological syndromes associated with the intervertebral disk are considered elsewhere in this text: the hypertrophic-hyperplastic changes in the dorsal annulus in canine cervical vertebral malformation—malarticulation myelopathy, and fibrocartilaginous embolic myelopathy, in which the intervertebral disk may be the source of the embolic material within the spinal cord and meningeal vasculature.

The intervertebral disk is a specialized joint between vertebral bodies (as are the articular processes between the arches) allowing for some degree of movement between two bones. The disk is also adapted for shock absorption, having a deformable central nucleus pulposus that is encircled by the lamellated, collagenous annulus fibrosus. If the nucleus degenerates, compressive forces that act on the disk are not transmitted uniformly from its center to the circumferential annulus fibrosus. As the annulus is thickest ventrally, protrusion of the nucleus occurs most commonly in a dorsal direction, towards the spinal cord. Disk extrusion may occur in a dorsolateral or even a lateral direction, impinging on the intervertebral foramen, nerve roots, and vertebral artery.³ Herniation cranially or caudally into the body of the vertebra occurs in humans, and the lesion so formed is referred to as a Schmorl's body or nodule. It seems to be quite rare in animals. If discharge occurs in a ventral direction, it displaces the ventral longitudinal ligament, inciting vertebral spondylosis.

Much of what we know of age-associated changes in the canine intervertebral disk was reported by Hansen in the early 1950s, and disk protrusions are often described as Hansen type I (extrusions, in which the annulus ruptures) and type II (bulges, which are milder). In **chondrodystrophic breeds** of dogs such as the **Dachshund** and **Pekingese**, a characteristic pattern of degenerative disk change is in train within the first few months of life.⁴ The nucleus pulposus (a remnant of the notochord) is normally loosely fibrillar and sparsely cellular with a metachromatic, mucoid matrix. In chondrodystrophoids, the nucleus is replaced by chondroid tissue, which mineralizes and disintegrates. Degenerative changes in the outer fibrous annulus soon follow. In contrast, clinical evidence of disk degeneration is not anticipated until middle age or beyond in the **nonchondrodystrophic breeds**, peaking at 6 to 8 years.⁵ In these dogs, degeneration begins in the annulus fibrosus with disruption of normal lamellar structure, hyalinization, and fragmentation. Collagenization of the nucleus is more common than is cartilaginous metaplasia. Intervertebral disk degeneration can result in bulging of an intact disk in which the nucleus herniates into, but is still retained by, the attenuated annulus. If the annulus is still partially preserved, a popular treatment now employed in humans (and attempted in a limited way in the dog) is to inject proteolytic enzymes into the nucleus to dissolve it and make it shrink. In contrast, if the nucleus ruptures through the annulus into the vertebral canal (Fig. 4-12), the disk is **extruded**. The most severe spinal cord injuries occur with sudden, severe disk extrusions. This is likely in the chondrodystrophic breeds. Furthermore, in the Dachshund and these other breeds, the vertebral canal is often stenotic, predisposing them to the risk of injury from a prolapse. In the thoracolumbar spinal cord, these can produce a functional or structural transverse lesion. If this occurs cranial to the L4 segment, the Schiff-Sherrington syndrome may result.

It is also reported that severe vertebral trauma can result in massive extrusion of a previously non-degenerate disk.⁶

Clinical presentation of canine intervertebral disk prolapse is quite variable, ranging from mild, subtle deficits to paraplegia or tetraplegia. Chondrodystrophic breeds may present at 2 to 3 years of age. Most prolapses occur between T11 and L3 (where much of the flexion of the vertebral column occurs), and so varying degrees of UMN and GP pelvic limb deficits are expected; cervical disk degeneration and protrusion produce these deficits in all four limbs. Disk protrusion is often painful, which may result from tissues impacted by the disk (nerve roots, meninges, ligaments) or the degenerate disk itself.⁷ Vertebral palpation can often localize an area of heightened sensitivity. Plain radiographs assist by revealing mineralized disk material in situ or prolapsed into the vertebral canal, as well as the presence of narrowed disk spaces. Myelography will further identify the site of spinal cord compression and that it is extradural. Magnetic resonance imaging is the procedure of choice in

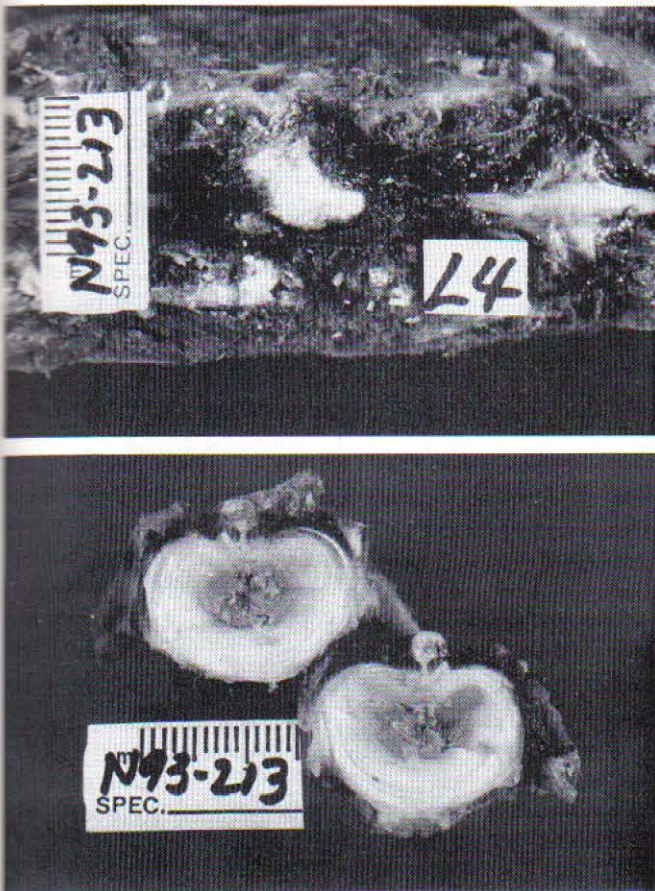


Fig. 4-12. Intervertebral disk prolapse, dog. **A**, L3-L4 prolapse into the vertebral canal and extensive hemorrhage from rupture of the vertebral venous plexus. **B**, Transected disk shows the degenerate and fragmented nucleus pulposus.

human medicine to diagnose intervertebral disk abnormalities and, where available, is applicable to the canine disease.

Examination of CSF reveals abnormalities in acute disk prolapse, but the fluid may be normal with a chronic injury. Consistent with spinal cord trauma, elevation of the protein level is more commonly found than increased numbers of cells in the CSF. A lumbar tap is more likely to yield abnormal fluid than a cisternal puncture.⁸

Pathological changes in the spinal cord caused by dorsal disk protrusions are found at the site of the prolapse and in the adjacent one or two segments. Sometimes the spinal cord is indented and flattened by the extruded disk material; in chronic protrusion, the dura may be adherent to the disk. Microscopically, a spectrum of changes are encountered in the spinal cord, and seemingly similar prolapses can induce quite different types and degrees of injury. A common manifestation of spinal cord compression is seen in the white matter of the dorsal, lateral, and ventral funiculi: Myelin sheaths are ballooned, and axons swell or are lost, giving

the tissue a rarefied or spongy appearance. This change has often been loosely referred to as demyelination, implying selective myelin loss, which is not the case; although some axons are demyelinated and survive, many are destroyed. Within a few days, macrophages appear within the myelin digestion chambers (best visualized in longitudinal sections of the tissue), and a fibrous astrocytosis develops in response to the neurodegeneration. With chronic compressions, perivenous fibrosis is found. Furthermore, loss of neurons from the gray matter may affect the dorsal, intermediate, or ventral horn populations.⁹ Knots of microglial cells mark the sites of cell body loss, and depletion of motor neurons results in Wallerian degeneration in the ventral roots. Discrete areas of malacia, mostly in the white matter and often in a bilaterally symmetrical pattern, may be found at and/or removed from the site of compression; they probably result from secondary vascular injury.¹⁰ Such lesions mature into cysts that contain a few gitter cells, newly formed small blood vessels, and slender glial processes that bridge the cavity. The most severe disk extrusions cause pannecrosis of gray matter and white matter.¹¹ In the acute stage, there are ghosts of ischemic neurons, hemorrhage, edema, and pallor of the tissue. The tissue progressively liquefies and becomes impossible to handle, preserve, and section. Vascular stasis inhibits significant leukocytic influx. Secondary to the transverse myelopathy resulting from the impact, Wallerian degeneration is found in spinal cord segments above and below the lesion in ascending and descending pathways. Mechanisms of traumatic spinal cord injury are discussed further in the introductory section of this chapter.

The level of the vertebral canal at which intervertebral disk prolapses occur is not random. Clinically, most prolapses involve the thoracolumbar region and, less frequently, the cervical region. For a number of reasons, the majority of thoracic vertebrae seem to be largely immune to disk prolapse: Limited flexion and extension are possible at this level of the vertebral column, which limits wear and tear; the vertebral canal is relatively spacious, compared to the diameter of the spinal cord; and these vertebrae are additionally braced by the intercapital (conjugal) ligaments, which run between opposite ribs, over the dorsal surface of the annulus, and below the dorsal longitudinal ligament. These factors all seem to be impediments to dorsal disk displacement between T2 and T11.

Dorsal extension of the disk may be in the midline, or it may deviate to the left or right, possibly resulting in asymmetrical neurological deficits. Disk material can rupture and herniate into the vertebral venous plexus. Sometimes, extruded degenerate disk material is found adherent to the dura. A small proportion of intervertebral disk protrusions (perhaps 5%) are associated with **ascending and descending myelomalacia**. The affected animal is tetraplegic, areflexic, and analgesic as a result of hemorrhagic or ischemic necrosis of the entire parenchyma of the spinal cord (Fig. 4-13). Severe subarachnoid hemorrhage is com-

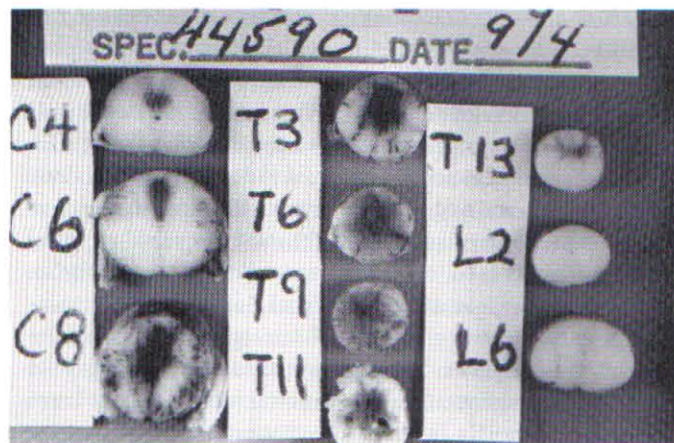


Fig. 4-13. Ascending myelomalacia, dog.

mon also. In very rare instances, this syndrome is encountered and yet no disk prolapse (or other abnormality) is found at necropsy. The pathogenesis of this myelomalacia is not known, save that the lesion is thought to reflect extensive compromise of intramedullary vasculature with hemorrhagic or ischemic infarction. Hypotheses have invoked catecholamines acting on intramedullary vessels or vasospasm of leptomeningeal vessels, which can be triggered by hemorrhage.

Intervertebral disk prolapse has been described in the horse, but the number of reports is few.¹²⁻¹⁶ Most have involved the cervical vertebrae, with affected horses presenting with acute tetraparesis and ataxia. The cat is curious, for degeneration and dorsal prolapse of intervertebral disks is said to be a common postmortem finding.¹⁷ In contrast, myelopathy resulting from disk prolapse in the cat is rare. Published cases have reported paraparesis or tetraparesis in cats ranging from 2 to 10 years of age with caudal thoracic or cervical prolapses.¹⁸⁻²⁰

References are on page 207.

POST-TRAUMATIC BLINDNESS AND OPTIC NERVE DEGENERATION IN THE HORSE

The consequences of head injury have been outlined in the general section on CNS trauma. Of all the domestic animals, horses are most prone to injury resulting from rearing up on the pelvic limbs and falling over backwards, striking the poll of the calvaria. Sometimes this results in fractures of the suture between the basisphenoid and basioccipital bones or fractures of the petrous temporal bone or tympanic bullae.¹⁻³ However, episodes have been observed (and a few recorded) in which such injury resulted in acute blindness in the absence of a skull fracture. At the time of injury, the affected horse usually remains conscious, may show epistaxis, and is acutely blind.⁴ Vision loss persists, with bilateral menace deficits and widely dilated pupils that are unresponsive to light. With time, optic disk pallor

and loss of retinal vasculature develop, although the electroretinogram remains normal.

Those cases that come to necropsy reveal a bilateral degeneration and atrophy of the distal optic nerves, involving the intraosseous portions and extending towards the optic chiasm. The affected portion is constricted and firm and (as shown microscopically) consists of necrotic myelinated axons, abundant foamy macrophages, and a thickened meningeal sheath. The adjacent nonconstricted tissue is better preserved, with vacuolated myelin sheaths and a proliferation of astrocytes.

This unique syndrome of optic neuropathy in the horse probably results from stretching of the optic nerves as the brain is accelerated toward the occiput at the time of impact. Edematous swelling probably leads to infarction of the intraosseous segment. In horses euthanized weeks or months after the event, orthograde Wallerian degeneration can be traced beyond the chiasm in the optic tract, and retrograde degeneration extends back to the eyeball. Other causes of equine optic nerve degeneration have been described.⁵

References are on page 207.

CALCINOSIS CIRCUMSCRIPTA AND SPINAL CORD COMPRESSION

Calcinosis circumscripta (equated by some with tumoral calcinosis) is an idiopathic disorder of focal soft tissue mineralization. The dog is most commonly affected, especially the German Shepherd, with subcutaneous deposits that sometimes are periarticular. In a unique form of calcinosis, tetraparesis has been observed in young dogs.

The dogs affected were 5- to 7-month-old Springer Spaniel, German Shepherd, and Rottweiler male puppies.^{1,2} Clinical histories were similar in all three dogs with about a 2- to 4-week course of progressive spastic tetraparesis and ataxia, with signs worse in the pelvic limbs. Survey radiographs identified a discrete midline calcified mass, situated between the atlas and axis in the area of the dorsal atlantoaxial ligament, with erosion of the atlas and the cranial part of the spine of the axis. Myelograms established compression of the dorsal aspect of the spinal cord at C1-C2 (Fig. 4-14). In all dogs, the discrete collagenous mass was surgically excised, resulting in rapid neurological improvement and return to normal gait within a few weeks. The discrete masses measured about 3 by 2 by 2 cm and consisted of white fibrous tissue bearing chalky calcium salt deposits. Microscopic examination was consistent with calcinosis, with a fibromyxoid mass sometimes merging into cartilage. There were focal areas of basophilic mineralization marked at the margins by epithelioid macrophages, multinucleated cells, and fewer neutrophils. In the two cases reported by Lewis and Kelly,¹ a malformed or small (hypoplastic?) spinous process of the axis was noted, whereas the mass reported by Marks and others² was located on the dorsal arch of C1 and extended under the cranial aspect of the spine of C2.

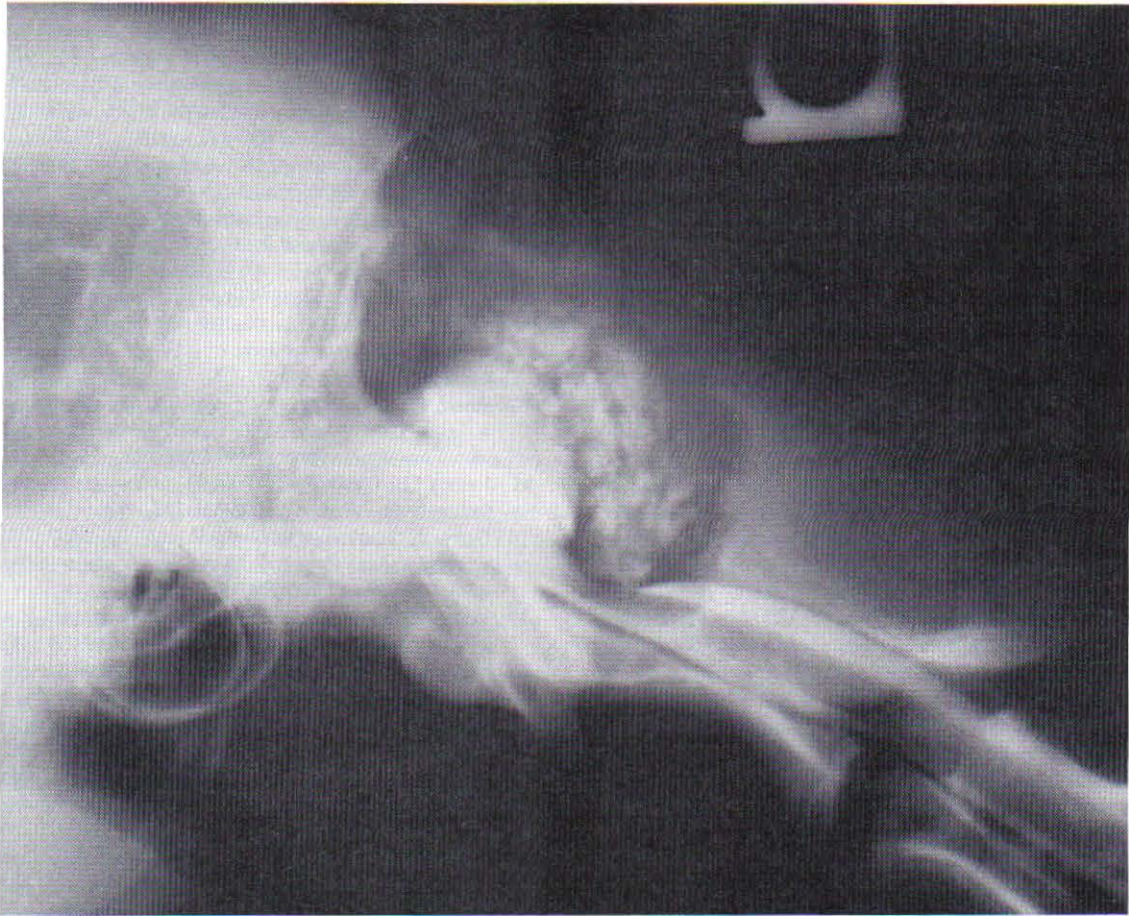


Fig. 4-14. Calcinosis cutis, dog. Myelogram reveals the soft tissue calcified mass between C1 and C2 that has destroyed much of the atlas and eroded the cranial aspect of the axis. Myelogram demonstrates spinal cord compression by the mass.

Tetraparesis and ataxia have been described in three young male dogs with a partially calcified mass of fibrous and cartilaginous tissue situated between the dorsal aspects of C1 and C2.³ This is probably a variant of this disorder.

Progressive paraparesis and ataxia were described in two young German Shepherd dogs, 6 and 7 months of age.⁴ Radiographic examinations in both dogs revealed a mineralized mass, dorsal to the articular processes at T2-T3, and situated between the dorsal spinous processes. Myelography demonstrated spinal cord compression at the level of the mass. Microscopic findings were of calcinosis circumscripta.

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Chapter 5 **DEGENERATIVE DISEASES OF THE CENTRAL NERVOUS SYSTEM**

Metabolic and circulatory disorders

HEPATIC AND RENAL ENCEPHALOPATHY

Hepatic encephalopathy (HE) is a severe neurological disorder that may develop in the absence of normal hepatic function. This scenario can occur in one of two ways:

1. As a result of congenital or acquired portosystemic vascular shunts, which deliver blood in the portal circulation directly into the caudal vena cava or azygous vein and so circumvent the liver
2. As a result of a diffuse, acquired liver disease

The pathogenesis of the encephalopathy of diffuse hepatic failure and that of portosystemic shunts may differ in some aspects, but for this discussion they are considered together.

Portosystemic shunts are now commonly recognized in the dog,¹⁻³ are somewhat less commonly encountered in the cat,^{4,5} and have been reported sporadically in other domestic species such as calves, foals, and pigs.⁶⁻⁸ Shunts may be **intrahepatic** or **extrahepatic**;⁹ the former are usually examples of a persistently patent ductus venosus and so are single and congenital. Extrahepatic shunts may be either congenital or acquired. Congenital, extrahepatic shunts are most commonly single aberrant communications between the portal vein (or one of its tributaries, such as the left gastric vein, splenic vein, cranial or caudal mesenteric veins, or gastroduodenal vein) and the caudal vena cava or azygous vein.⁹ In contrast, acquired portosystemic shunts are usually multiple and tortuous; they develop typically as a consequence of portal hypertension from chronic, progressive hepatitis with cirrhosis. The exceptions are the rare examples in young dogs with (presumed) congenital arteriovenous (arterioportal) fistulae, in which portal hypertension, ascites, and extrahepatic portocaval shunts develop.¹⁰

Dogs and cats with congenital shunts are usually presented by 2 years of age, often within the first months of life, and sporadically at any age.¹¹ Concerns of their owners commonly relate to a neurological disorder, although gastrointestinal or urinary tract signs may be noted. Excessive salivation is common in affected cats. Affected animals may be small for their age and in poor nutritional condition. Although this is a diffuse encephalopathy, CNS signs are chiefly referable to the prosencephalon: They include various expressions of bizarre behavior—staring into space, inappropriate vocalization, aggression, agitation, propulsive walking or circling—and also depression, lethargy, head pressing, ataxia, blindness, collapse, and coma. Classically these signs wax and wane from day to day, and in many cases they can be precipitated by feeding, especially a high-protein diet. Imaging studies may reveal a small liver, the aberrant venous channel, and sometimes enlarged kidneys. In some cases, ammonium biurate crystals are found in the urine. Clinical chemistry studies include a search for elevated levels of fasting and postprandial bile acids, elevated blood ammonia or an abnormal ammonia tolerance test,¹² and excessive sulfobromophthalein retention. Mesenteric venograms serve to confirm the diagnosis by demonstrating the shunt and establish the options for surgical or medical management of the case. In congenital shunts, failure of normal hepatic portal vascularization deprives the liver of nutrients and trophic factors such as epidermal and fibroblast growth factor and pancreatic insulin and glucagon. Histopathological examination of such livers reveals small hepatic acini with a dearth of portal venous branches and a compensatory proliferation of hepatic arterial branches in the triads.

Hepatic encephalopathy associated with severe, acquired hepatic degeneration and necrosis is most common in adult animals. In the United States, however, an episode of hepatic toxicosis occurred in neonatal foals that had been administered a (presumed toxic) microorganism culture after birth, resulting in the clinical and pathological development of HE.¹³ Most cases in mature ruminants and horses result from grazing plants that contain pyrrolizidine alkaloids.^{14,15} Other hepatotoxic associations with HE include lupinosis,¹⁶ facial eczema,¹⁷ woolly everlasting daisy toxicity,¹⁸ and signal grass toxicity.¹⁹ Spongy vacuolation has also been found in the brains of sheep with chronic copper poisoning, in which condition there is liver injury, but these may be episodes of renal rather than hepatic encephalopathy, resulting from hemoglobinuric nephrosis (see later in this section). Horses also develop HE from Theiler's disease (serum hepatitis), a presumed viral hepatitis of the horse. Animals with severe destructive hepatic disease may show signs of acute or chronic hepatic failure (wasting, jaundice) as well as neurological signs. Sometimes CNS signs predominate, as in horses with Theiler's disease (which may be maniacal); in other animals, neuraxial changes are clinically silent. In horses with HE, there is a remarkable disparity between the severity of the clinical signs and the subtlety of the pathological changes in the brain.

In animals that succumb with HE or are euthanized, gross neuropathological changes are lacking. Microscopic

changes recognized are twofold: (1) polymicrocavitation or spongiform change of white matter and (2) single or small groups of astrocytes with clear, swollen nuclei, which are referred to as Alzheimer type II cells. Whether either or both changes are present in HE varies from species to species. In the horse, changes are limited to the development of Alzheimer type II cells, whereas it seems that both changes occur in all the other domestic animals. Often the polymicrocavitation is the most obvious alteration, and sometimes it is the only change described or recognized.

In HE, **polymicrocavitation** occurs diffusely throughout the neuraxis and, consistent with a metabolic disorder, has a bilateral and symmetrical distribution. The lesion is located in white matter and (reminiscent of central pontine myelinolysis of humans) conspicuously involves myelinated bundles of fibers that are interspersed with gray matter. Cerebral hemispheric involvement is found in the peripheral fibers of the corona radiata at the junction with the gray matter and in the adjacent deep cortex (Fig. 5-1, A). Vacuolation is found also in the internal capsule, thalamus, hypothalamus, cerebellar medulla and peduncles, and pons and medulla oblongata (Fig. 5-1, B). Lesions of the spinal cord are found in the fasciculus proprius (at the junction of gray and white matter). Vacuolated myelin appears to be stable, does not incite a histiocytic response, and can be viewed as a cytotoxic edema. Consistent with this interpretation is the observation that the vacuolation regresses if the

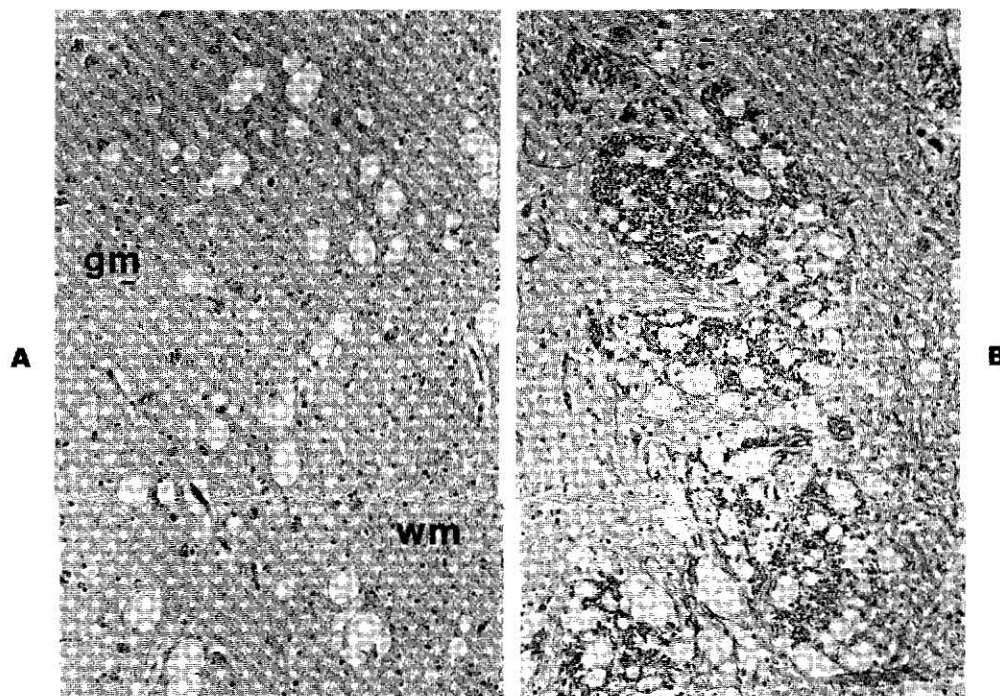


Fig. 5-1. Hepatic encephalopathy, cow. **A**, Vacuolation at the junction of cerebral gray matter (*gm*) and white matter (*wm*). (H&E, $\times 140$.) **B**, Vacuolation of myelinated fibers in medulla. (H&E, $\times 140$.)

stimulus is removed.²⁰ Little is published on the ultrastructural changes in spontaneous HE, but experimental studies, employing ammonia infusion, have shown that the spongiosis can result from ballooning of myelin sheaths which split at the intraperiod line.²¹

Alzheimer type II astrocytes are found as single, paired, triplet, and occasionally large groups of swollen, open-faced, vesicular astrocyte nuclei in the gray matter (see Fig. 5-2). Ultrastructurally, they contain a variety of nuclear bodies (which are found in a number of pathological disorders) and glycogen particles.²² They are most numerous in the neocortex, basal nuclei, and hippocampus, as neuronal satellites, or isolated in the neuropil. The cytoplasm of these cells is inconspicuous and GFAP staining is weak or negative, although S-100 expression is retained.^{23,24} This suggests that HE results in selective loss of GFAP filaments, which is unusual as reactive astrogliosis is invariably associated with increased cytoplasmic filament content. The effects of ammonia on astrocytes in culture have shown both reactive (proliferation of mitochondria and smooth endoplasmic reticulum) and degenerative (accumulation of dense bodies, reduced GFAP content) changes.^{25,26} Lacking an effective urea cycle, CNS tissue metabolizes ammonia by way of the astrocytic enzymes glutamine synthetase and dehydrogenase.^{25,27} The basis for the changes in proto-

plasmic astrocytes, which result in the formation of Alzheimer type II cells, is uncertain. Norenberg and colleagues' studies^{25,26} provide evidence for a direct toxic effect of ammonia on these cells.

Investigators have attempted to unravel the pathogenesis of HE for decades. Theoretically, CNS disease could result from a loss of normal hepatic detoxifying function or failure to synthesize a crucial neural metabolite. Studies have focused on the former, and multiple factors have received attention,²⁸⁻³⁰ although some are given more credence than others. The importance of **hyperammonemia** seems to be broadly accepted, although experimental infusions with ammonium salts do not recapitulate all aspects of HE. Ammonia is normally produced by bacteria in the colon that degrade urea from dietary protein. Antibiotics (which depress the alimentary flora) reduce this conversion and so diminish the neurological disorder. In fact, affected dogs or cats have sometimes been thought to have an antibiotic-sensitive bacterial encephalitis or meningitis. Ammonia delivered to the liver via the portal vein is normally detoxified. With portosystemic shunts or severe hepatic insufficiency, elevated blood levels of ammonia result. Some is excreted in the urine, resulting in the formation of ammonium biurate crystals or calculi. Ammonia in the CNS is metabolized by astrocytes to glutamine, which itself may be neurotoxic.

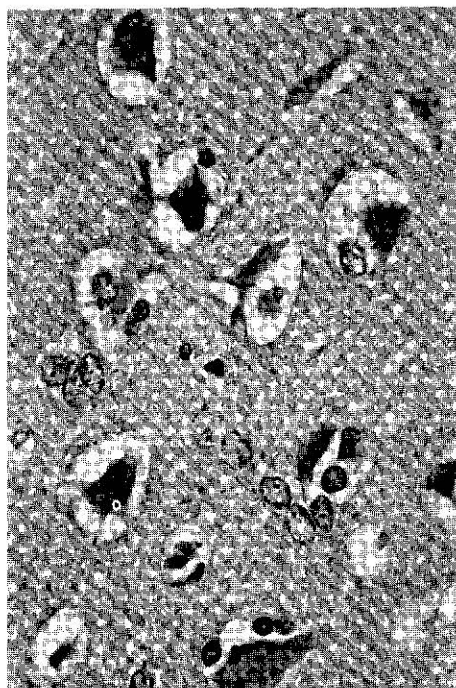


Fig. 5-2. Renal (uremic) encephalopathy, foal. Alzheimer type II astrocytes in cerebral cortex. (H&E, $\times 560$.)

Other putative toxic factors are **short-chain fatty acids** and **mercaptans**. Blood composition of **amino acids** alters, with a reduction of branched-chain amino acids and increased aromatic amino acids. The latter include phenylalanine, tyrosine, and tryptophan; tryptophan in particular is toxic to the CNS. Tyrosine can give rise to octopamine, which, with other amino acids, could act as **pseudotransmitters** within the CNS. It was proposed that such could result in altered neural activity, but this theory now has fewer supporters. Bacterial synthesis of **γ -aminobutyric acid** in the alimentary tract is also heightened; as this is a powerful inhibitory neurotransmitter, the imbalance of excitation and inhibition may be important. Alterations in the binding sites for excitatory amino acids have been demonstrated in dogs with HE.³¹ Changes in the **blood-brain barrier** in HE, permitting access to the CNS of substances that normally would be excluded, are often invoked. In summary, the pathogenesis of HE may be multifactorial,³² perhaps with several factors acting in synergy.

In humans, an encephalopathy subsequent to the development of severe renal failure is well recognized (**uremic** or **renal encephalopathy**), but very few cases have been described in the veterinary literature. The neurological aspects of renal disease in three dogs are discussed by Wolf.³³ Howell and others recorded their observation of status spongiosis in the brains of five of eight uremic dogs.³⁴ The neuropathology of renal encephalopathy has been described in one cow with chronic, diffuse interstitial nephritis³⁵ and in two woodchucks with severe renal disease.³⁶ Microscopic changes in the animals in these two reports were of polymicrocavitation but lacked Alzheimer type II cells. A horse we have observed with renal encephalopathy had prominent Alzheimer type II astrocytes (Fig. 5-2), and these cells did not express GFAP—exactly as occurs in horses with hepatic encephalopathy.

White matter polymicrocavitation has been observed in the CNS of sheep with **chronic copper poisoning**. In this disorder, there is progressive hepatic injury as copper accumulates in the liver, and terminally there is release of large quantities of copper from the liver, massive intravascular hemolysis, and hemoglobinuric nephrosis. It is perhaps a moot point whether the spongiform change is primarily a consequence of hepatic or renal failure, but we suspect that it may be the latter. This lesion has been studied in experimentally induced copper poisoning in sheep.³⁷ Ultrastructural studies that attempted to explain the basis for the spongiform change came to differing conclusions: that it results from intramyelinic vacuolation³⁸ or that it results from swelling of the outer tongue of oligodendrocyte cytoplasm.³⁴

Urea is used as nitrogenous supplement in the food of ruminants, and ammonium salts have been used to this same end. Excessive consumption of either can result in peracute to acute ammonia poisoning.^{39,40} Hyperammonemia can also result from inherited deficiencies of the enzymes of the urea

cycle, and these are discussed with the disorders of intermediary metabolism.

References are on page 327.

DISORDERS OF INTERMEDIARY METABOLISM

There are in humans a large number of inborn disorders of intermediary metabolism that are expressed clinically as neurological disease.¹ Only a few are described in domestic or laboratory animals, but the history of comparative medicine suggests that more await to be recognized. In these disorders, mutations in enzymes result in deranged metabolism of specific cellular constituents such as amino acids or carbohydrates. In some cases, the disorder affects enzymes within a specific organelle, such as a peroxisome or a mitochondrion.²

In the **aminoacidopathies**, there are inherited deficiencies of specific enzymes involved in amino acid metabolism. Affected children are often symptomatic from birth, and in these neonates secondary changes (metabolic acidosis, hyperammonemia) are of major importance. The clinical picture varies from listlessness to seizures to mental retardation. The neuropathological changes are of spongiosis of white matter, deficient myelination, and astrogliosis. The most important aminoacidopathy of humans is **phenylketonuria**, of which there are several subtypes. There is impaired hydroxylation of phenylalanine (and in some forms a missing cofactor), the disorder being acquired as an autosomal recessive trait. This is one disorder for which all newborn children are screened; dietary therapy is instituted as needed. White matter changes can be detected by magnetic resonance imaging.³ **Maple syrup urine disease** is a disorder in the metabolism of the branched-chain amino acids leucine, isoleucine, and valine, which, with their respective ketoacids, accumulate. The characteristic maple syrup odor of urine is from isoleucine. Affected infants appear normal at birth but soon are lethargic, feed poorly, and have seizures. A clinically, pathologically, and biochemically similar disorder occurs in **Hereford calves**.⁴ Animals affected may be bright and suckle strongly from birth or may be immediately dull. Within 1 to 3 days there is rapid deterioration to recumbency, opisthotonus, paddling, and death. The histopathological findings are severe white matter spongiosis throughout the neuraxis. Deficient activity of branched-chain ketoacid decarboxylase has been demonstrated. This bovine disorder is discussed more fully with the spongiform encephalopathies; it represents the disorder originally described by Cordy as hereditary neuraxial edema in Hereford calves. Further human aminoacidopathies with neurological sequelae are **hyperglycinemia**, **aspartylglycosaminuria**, and **homocystinuria**. There are several patterns of **tyrosinemia** in humans, and mental retardation may result. In animals with tyrosinemia (a dog, mink) only ocular, cutaneous, and urinary lesions have been observed.^{5,6}

Hyperammonemia resulting from developmental or acquired portosystemic shunts is discussed under hepatic encephalopathy. Inherited disorders of the **urea cycle** also interfere with the normal degradation of ammonia, resulting in hyperammonemia and encephalopathy. In humans, enzyme defects at each step of the cycle have been identified. Two unrelated dogs are described in which the analysis of liver biopsies revealed deficiency of **argininosuccinate synthetase**.⁷ The clinical complaints in these two animals included chronic diarrhea, depression, and excessive sleepiness. Both had elevated blood ammonia levels in the face of normal sulfobromophthalein excretion times. Harper and associates have identified an acute, fatal, neurological disorder of **Friesian calves** in Australia with markedly elevated plasma citrulline levels and argininosuccinate synthetase deficiency.⁹ This enzyme catalyzes the amalgamation of citrulline and aspartate into argininosuccinic acid. In **bovine citrullinemia**,^{10,11} 1- to 5-day-old calves, which are normal at birth, become suddenly depressed, apparently blind, tremor and head press. Recumbency, seizures, coma, and death ensue within 4 to 6 hours. Histologically there is a diffuse, moderately severe hydropic change in hepatocytes. The brain grossly is unremarkable but shows cerebral cortical edema involving mostly the deep laminae. Perivascular and perineuronal spaces are enlarged, giving the gray matter a modest spongiform appearance (Fig. 5-3). In these areas, astroglial nuclei are enlarged and vesicular. Ultrastructural examinations have shown astroglial swelling consistent with intracellular edema.¹² Citrullinemia has also been recognized in Friesian calves in New Zealand, presumably introduced with semen from a carrier bull.¹³ Changes in synaptosomal uptake and release of neurotransmitters in calves with maple syrup urine disease and citrullinemia have been compared.¹⁴

In humans, disturbances in the metabolism of carbohydrate are important (**galactosemia**), and several congenital encephalopathies are associated with **metabolic acidosis**. Some involve organic acids such as methylmalonic, isovaleric, and propionic, for which there may be, respectively, methylmalonyl-CoA mutase, isovaleryl-CoA dehydrogenase, or propionyl-CoA carboxylase enzyme deficiencies. Lactic acidemia may result from deficiencies of pyruvate carboxylase, pyruvate decarboxylase, and other enzymes. Elevated levels of blood lactic and pyruvic acids are found in **Leigh's disease** or **subacute necrotizing encephalomyelopathy**, a mitochondrial disorder. We have encountered a neurological disorder in **Alaskan Husky dogs** with lesions remarkably similar to those in Leigh's disease in humans.¹⁵ This unusual clinical syndrome developed in a 2-year period involving 4 dogs from 3 litters in a kennel of about 200 Alaskan Huskies raised as racing sled dogs. Three of these dogs were autopsied. The commencement of clinical signs was usually a fairly abrupt onset of ataxia starting from 6 to 9 months of age. Two dogs became unable to get up after a few days. The description of their signs suggested a problem with balance and coordination (vestibular-cerebellar) and unusual anxiety. The other two dogs progressed slowly over a period of 1 to 4 months of observation. Clinical signs included hypermetria of all limbs, loss of balance, spasticity, anxiety, and a tendency to show propulsive exploratory behavior, mild head tremor, partial to complete loss of vision with normal pupil size and light response, and pronounced hypalgesia of the nasal septum, mouth, and pharynx, with a significant difficulty in prehension of food. These signs reflected a diffuse brain disturbance. Cerebrospinal fluid was normal.

On autopsy, the transverse sections of the brain of the more severely affected dog that was still ambulatory showed

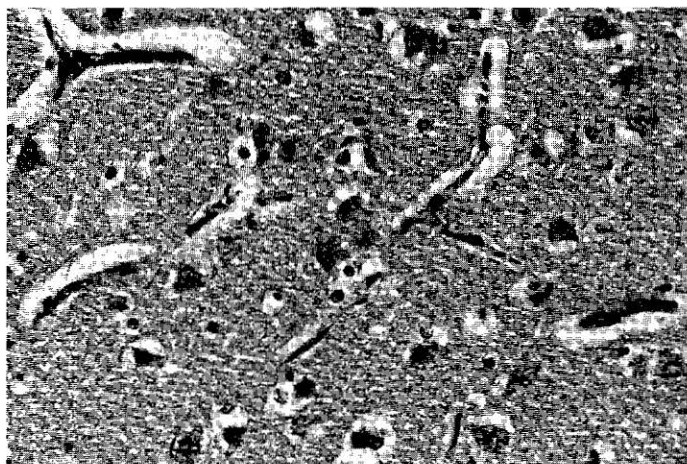


Fig. 5-3. Citrullinemia, calf. Mild astrocyte swelling (perivascular astrocyte foot processes), cerebral cortex. (H&E, $\times 350$.)

an extensive bilaterally symmetrical soft gray cavitation (Fig. 5-4) extending from the thalamus to the medulla. It was most extensive in the thalamus, where it affected more than a third of the parenchyma. The cavitation had a V-shaped oblique appearance resembling the extended wings of a butterfly. This malacia was continuous caudally through the brain stem, where it narrowed considerably. On microscopic examination, the cavity was bordered by extensive reactive astrogliosis, capillary hyperplasia with endothelial cell hypertrophy, and collections of macrophages. On the extreme edges of the lesion, normal-appearing neuronal cell bodies were surrounded by degenerate neuropil. In these same areas, axons were also preserved. In the pons and medulla, where the neuropil degeneration was less extensive, the entire lesion consisted of reactive astrocytes, macrophages, proliferated capillaries, and numerous spared axons and neuronal cell bodies. In numerous areas of dorsal and lateral neocortex, a laminar degeneration occurred in a short arc at the depths of sulci. This predominated in the middle and deep laminae and included the presence of ischemic neuronal degeneration. A similar cortical degeneration occurred in a few folia of the cerebellar vermis.

This unique degenerative lesion has a remarkable resemblance to infantile subacute necrotizing encephalomyelopathy of children, also designated as Leigh's disease. This disease is an inherited enzyme deficiency that interferes with the ability to metabolize thiamine for its use as a coenzyme. This typically results in the accumulation of pyruvate, lactate, and alanine in the serum and CSF. In some forms, there is a deficiency of respiratory chain enzymes as well. The mitochondrial location of these biochemical reactions has implicated this as an example of a mitochondrial encephalopathy. This is inherited as an autosomal recessive gene in children. The occurrence of this similar disease in

one kennel of related line-bred Alaskan Huskies implicates an inherited basis. There are common ancestors in all three litters.

The only other report of a similar disease in domestic animals was in **kittens**¹⁶ that showed a fine whole-body tremor by 1 month of age. The tremor progressed along with cerebellar signs and terminated with visual loss and seizures at 3 months of age. Brain stem and spinal cord lesions were similar to those described in Leigh's disease. Blood pyruvate and lactate were elevated, but no enzyme deficiency was reported. The disease was inherited as an autosomal recessive defect.

A unique bilaterally symmetrical nuclear neuropil degeneration was diagnosed in two related young **Australian cattle dogs**. Both had a brief history of seizures at a few months of age, followed by a progressive gait deficit in all four limbs. One dog that was maintained to 2 years of age progressed to a tetanic-like caudal extension of both forelimbs. The degenerative process was most pronounced in the cervical intumescence followed by the lumbosacral intumescence. No other spinal cord segments were affected. Bilateral lesions also occurred in the lateral cuneate, vestibular and cerebellar nuclei, nucleus ambiguus, and caudal colliculi. An inherited metabolic abnormality is presumed.

A group of human metabolic neurological conditions that have "emerged" in the last decade or so are the **peroxisomal disorders**.¹⁷⁻¹⁹ Peroxisomes (microbodies) are variably sized cytoplasmic organelles with a homogenous granular matrix, a dense nucleoid (lacking in humans), and a single limiting membrane. They are found in most cells (plant and animal) and can participate in many metabolic pathways. Peroxisomes contain more than 40 enzymes, but they characteristically employ oxidases on their substrates, forming hydrogen peroxide that they can degrade by catalase. They



Fig. 5-4. Alaskan husky encephalopathy. Bilateral cavitation in the thalamus. (Luxol fast blue, cresyl echt violet, $\times 5$.)

were named because of this peroxidase-based reaction, but many other oxidative activities are now known. Peroxisomes play a major role in the β -oxidation of very-long-chain fatty acids, and peroxisomal disorders are marked by reduced catabolism of cholesterol and deficient oxidation of very-long-chain fatty acids. Drugs used to treat hyperlipidemia induce the proliferation of peroxisomes. In peroxisomal disorders, there may be (1) reduced numbers of peroxisomes and their total enzyme pool, (2) normal numbers of peroxisomes but a diminished enzyme complement, or (3) normal numbers of peroxisomes and a single enzyme deficiency. A number of neurological diseases are now known to be peroxisomal disorders. These diseases include **Zellweger's syndrome** (cerebrohepatorenal syndrome), **neonatal adrenoleukodystrophy**, **hyperpipecolic acidemia**, and **infantile Refsum's disease**, which fit into the first category of peroxisomal disorders; pseudo-Zellweger (category 2); and **X-linked adrenoleukodystrophy** (category 3).¹⁷⁻¹⁹ Defective myelination is a feature of the group, and it may be significant that these organelles are particularly numerous in oligodendrocytes before the onset of myelin synthesis.²⁰

Primary **mitochondrial diseases** have been known in humans since the 1960s. These can now be classified as myopathies, encephalomyopathies, and encephalopathies.² Clinically, there is considerable overlap among the syndromes. Various structural changes in mitochondria are recognized (size, shape, inclusions); metabolic dysfunctions include disorders of substrate transport and of utilization, oxidation, and phosphorylation coupling and deficiencies of the respiratory chain complexes.

The newborn infant undergoes considerable physiological erythrolysis, which is amplified if there is blood group incompatibility. If the bilirubin generated cannot be conjugated and excreted in bile, **bilirubin encephalopathy** (kernicterus) may ensue. The Gunn rat has a congenital deficiency of hepatic UDP-glucuronyl transferase, is unable to conjugate bilirubin and glucuronic acid, and in some animals an encephalopathy develops.²¹ The neuropathological changes in these rats are degeneration of cerebellar Purkinje cells and later of other neuronal populations. In affected infants, the brain is appreciably yellowed, and there is necrosis of basal and brain stem nuclei.

References are on page 328.

LYSOSOMAL STORAGE DISEASES

Introduction—general principles

Sphingolipidoses

Gangliosidoses

Globoid cell leukodystrophy

Metachromatic leukodystrophy

Gaucher's disease

Niemann-Pick disease

Glycoproteinoses

Fucosidosis

Mannosidosis

Galactosialidosis

Mucopolysaccharidoses

Miscellaneous

Glycogenoses

Ceroid lipofuscinosis

Introduction—General Principles

Lysosomes are the membrane-bound cytoplasmic organelles found in virtually all cells and largely responsible for the catabolic activities that are obligatory in biological systems. These bodies form a sequestered pool of hydrolytic enzymes that can degrade both effete cellular constituents and extracellular materials acquired by phagocytosis or pinocytosis. Lysosomal enzymes are biochemical catalysts that, operating optimally at low pH, are referred to as **acid hydrolases**.¹ In the process of autophagy, polymers of host-derived glycoproteins, polysaccharides, or complex lipids from senescent organelles are compartmentalized in an autophagosome. This vacuole fuses with a primary lysosome, and within the secondary lysosome so formed these complexes are dismantled in a step-wise fashion, yielding their basic monomeric constituents, which can be reused. Indigestible debris remains as a **residual body**. Should a particular enzyme be lacking (or for other reasons inoperative), the catabolic degradation of the substrate is interrupted, and the partially disassembled compound accumulates within the lysosomes (hence "storage" diseases). The hallmark of these diseases is that a specific lysosomal enzyme is defective or for other reasons inoperative and, as a consequence, its individual substrate(s) accumulates.² Occasionally the defect lies with an **activator protein** that may solubilize and complex with the substrate, rendering it recognizable by the hydrolase.³ The morphological expression of these cellular derangements is the presence of large cytoplasmic inclusions containing undigested material. A lysosomal basis is substantiated by a positive reaction for acid phosphatase in histochemical preparations and by demonstrating, at the ultrastructural level, that the cytosome has a single limiting membrane.⁴

Most lysosomal storage diseases are genetic disorders. All cells in the body, for which the gene in question encodes the defective or missing protein (an enzyme), are affected. It does not follow, however, that all organs manifest the defect equally. If the missing hydrolase catalyzes a step in the breakdown of a plasmalemmal ganglioside, neurons of the CNS (rich in these glycolipids) are particularly compromised. In the mucopolysaccharidoses, substrate predictably accumulates in connective tissues, as well as in neural tissues. Neurons are afflicted in most of these diseases because these are post-mitotic, permanent cell populations. Because cells of the monocyte-macrophage system are

professional scavengers that take up extracellular materials (heterophagy), they too are prone to develop storage problems. Involvement of fixed macrophages, particularly in lymphoid organs, occurs in some of these diseases. In some lysosomal disorders, for example, GM₁ gangliosidosis, different substrates are stored in neural and visceral tissues.

Since 1965, when the principles of the lysosomal storage diseases were first espoused,⁴ it has become clear that there are a number of ways in which the normally smooth-functioning of lysosomal organelles can go astray. These rearrangements as summarized by Alroy and colleagues,⁵ Evans,⁶ and others⁷ include the following:

1. The enzyme is not synthesized.
2. The enzyme is synthesized but is biologically inactive or unstable.
3. The enzyme is synthesized, but its activator or protector protein is lacking.
4. The active enzyme is synthesized but fails to be compartmentalized within the lysosome.
5. There is a failure of transport of material across the lysosomal membrane for further degradation in the cytosol.
6. There is uptake of materials that can inhibit specific lysosomal hydrolases.
7. There is uptake of materials that lysosomes cannot degrade.

The underlying defect in the hosts' genome varies among these many diseases to be discussed. Whereas gene deletion would result in failure of enzyme synthesis, mutation would rather lead to the manufacture of a defective enzyme. As for most biological functions, normal levels of these hydrolases well exceeds minimal needs, and heterozygote carriers, with approximately half of the enzymatic activity of normal animals, fail to show clinical deficits. Homozygous affected animals often have trace activity, perhaps 2% to 5% of the norm, and at such severe levels of depletion show substrate accumulation and clinical signs. Interestingly, in affected animals, the activities of other lysosomal enzymes are often elevated, perhaps reflecting nonspecific stimulation (if this is possible) or the simple hypertrophy of the cellular lysosomal apparatus. If an activator protein is lacking, the enzyme that is catalytically deficient may also be present in elevated measure (for example, in GM₂ gangliosidosis AB variant).

Clinically, the lysosomal storage diseases are a diverse group of progressive, lethal, multisystemic disorders of animals and humans. Involvement of the CNS is common, and so neurological disorders are to be anticipated. There are few exceptions, such as the glycogenoses, which primarily produce weakness and cardiac failure.⁸ Many are known to be transmitted as autosomal recessive traits⁹ (X-linked patterns are also recognized in humans) and represent specific gene mutations. A few clinically and pathologically similar conditions are acquired by virtue of exposure to neurotoxic substances that inhibit specific lysosomal activ-

ities. It can be argued that in these inherited diseases, there is perhaps the closest homology between spontaneous disorders of animals and humans. For any specific condition, the phenotypic spectrum that is recognized is often broader in humans. Thus, in people, infantile, juvenile, and adult-onset forms¹⁰ are often identified. Further, it has been found that for a few specific lysosomal enzyme deficiencies, there are differences between humans and animals in the composition of the stored materials. However, with these caveats, it seems likely that many of these disorders that afflict domestic or laboratory animals can be viewed with some confidence as bona fide models of human disease (a much abused term). Indeed, it seems very reasonable that such spontaneous disorders in animals should be utilized to explore the possibilities for prenatal diagnosis, to delve into matters of pathogenesis, and to evaluate the range of therapeutic options for these diseases.^{5,11}

The characterization of a lysosomal storage disorder progresses in a predictable way from the identification of a characteristic clinical disorder, through the description of the associated pathological changes in tissues, and ultimately to the crucial biochemical studies that identify the enzyme deficit and the stored substrate. Biochemical analysis is required for the definitive diagnosis, and it is important to bear this in mind (and freeze unfixed specimens) at the time of the necropsy. These diseases have been named in a variety of ways. Historically, some in humans are named for the physicians who first recognized a characteristic clinicopathological entity in their patients; examples are Tay-Sachs and Niemann-Pick diseases. Generally they are now designated by the defective acid hydrolase or the primary stored substrate, subclassified where necessary, for example, mucopolysaccharidosis types 1 to 7. A few lysosomal disorders have particularly dire effects on the central and/or peripheral myelin-forming glia; this group is known as the leukodystrophies, although not all leukodystrophies are known to be lysosomal disorders.

Historically and clinically, these disorders have many common features and there are clues that can assist in reaching a presumptive diagnosis:

1. Many are inherited as autosomal recessive disorders from clinically normal, heterozygous parents, and so perhaps one to three affected animals in a litter can be anticipated. From a mating of carrier male and female parents, homozygosity with clinical disease would be expected in 25% of the litter.
2. The index of suspicion is raised if a specific breed, in which a recognized lysosomal disease occurs, is involved. Prior history may indicate similar disorders from the previous progeny of the same parents.
3. Sometimes there is a history of neonatal deaths. Further, affected animals, if viable, are likely to grow more slowly than their phenotypically normal littermates.
4. With few exceptions (one being β -mannosidosis in

goats), such animals are usually normal at birth and slowly develop clinical signs within the first few weeks or months of life. Exceptionally, the onset of clinical signs is in adulthood, as in ceroid lipofuscinosis in Dachshunds and GM₂ gangliosidosis in the Japanese Spaniel dog. These signs usually reflect neurological derangements⁶ and include ataxia (often cerebellar), tremor, behavioral changes (apprehension, aggression), seizures, and blindness. In some storage disorders, namely, the mucopolysaccharidoses, skeletal and connective tissue changes are prominent. Where visceral storage occurs, hepatomegaly and splenomegaly may be present.

5. Pedigree analysis, often of geographically widely scattered affected animals, commonly incriminates a single sire, his siblings, or his immediate progeny. This is because favored sires are often used widely for natural or artificial breeding programs, typically in dogs, cats, and cattle. Furthermore, with the availability of embryo transfer and the international movement of animals, lysosomal storage diseases can be introduced into countries in which they have not previously been recognized. With the short generation time in domestic animals and, in some circumstances, a tendency toward inbreeding,¹² a relatively high frequency of the deleterious gene can result, especially if the sire is used early in the development of the breed. Jolly has discussed this "founder" effect on some genetic diseases of cattle.¹³

In these diseases, a common theme is played out in affected tissues. As cellular lysosomes become progressively filled with substrate that they cannot further degrade, they become swollen and more conspicuous. This relentless process begins during fetal life; indeed, characteristic storage lesions have been discerned in fetal tissues,¹⁴ including the fetal membranes. In paraffin-embedded specimens prepared for light microscopy, intracellular storage imparts a granular or vacuolar quality to the cytoplasm. This reflects the solubility of the accumulated metabolite in water or the organic solvents used to facilitate tissue permeation with paraffin wax. Soluble materials leave an empty vacuole, perhaps at the electron microscopic level to be visualized as residual flocculent or granular profiles. Experimental studies in laboratory animals, employing exogenous inhibitors of specific lysosomal hydrolases,¹⁵ have shown that in some tissues storage vacuoles may form after only 5 days. It is generally held that neurons are unable to rid themselves of normally accumulating residual debris, as attested to by their characteristic complement of lipofuscin with progressive aging. During some acute chemical intoxications, cytoplasmic processes of glial cells have been observed probing deeply into the somata of neurons, apparently removing lysosomal dense bodies,¹⁶ and Glees¹⁷ has suggested that microglial cells can remove osmiophilic granular wastes from neurons. Discharge of lysosomal bodies from hepatocytes in feline

GM₂ gangliosidosis has been recorded.¹⁸ Despite these observations, common experience shows that in storage diseases, cells including neurons that are embarrassed by complex polymeric compounds they are unable to catabolize normally, accumulate the substrate and consequently swell. Cytomegaly is often evident in light microscopic preparations and sometimes is sufficient to produce organ enlargement (liver, spleen).

It is natural to enquire how this lysosomal indigestion perturbs cell function and so results in a clinical disorder. This question has not been satisfactorily answered, but several proposals have been made. Progressive filling of the cytosol with swollen secondary lysosomes must mechanically impede intracellular traffic, but the importance of this is not known. The stored material may be cytotoxic, as appears to be the case in globoid cell leukodystrophy, in which condition oligodendrocyte necrosis results in a primary demyelinating process. Certainly in these diseases some neurons in the CNS die, apparently as a consequence of lysosomal storage, but this occurs most consistently in a few populations, such as cerebellar cortical Purkinje cells. A different pathophysiological perspective has emerged from studies initiated by Purpura¹⁹ and continued by Walkley and associates.²⁰ These investigators, who have extensively utilized Golgi preparations to study three-dimensional aspects of neuronal structure, have revealed an array of structural modifications common to spontaneous and induced storage diseases. In certain neuronal populations, particularly the pyramidal cells of the cerebral cortex, they found that fusiform enlargements (meganeurites) with ectopic secondary dendrites are formed just proximal to the initial axon segment. New synaptic formations are found associated with these redundant structures,²¹ which must have implications for disturbed neuronal function. Singer and colleagues have proposed that disturbances in synaptic function could occur in the gangliosidoses as gangliosides are normally concentrated within synaptic plasma membranes and are involved in synaptic transmission.²² Another important factor is the focal axonal swellings (spheroids) (Fig. 5-5) within myelinated and unmyelinated fibers that occur with varying frequency in this group of diseases. As many of these dystrophic axons affect inhibitory GABAergic fibers, they may be particularly important in producing CNS dysfunction.²³ Ultrastructurally, such ballooned axons are distended with intact and degenerating mitochondria, membrane-bound dense bodies, tubulovesicular profiles, and a minor component of cytoskeletal elements. Typically they contain little or no lysosomal storage material, this being confined to the neuronal soma and primary dendrites. Their development may reflect the accelerated formation of cellular debris and/or its failure of retrograde transport to the perikaryon for digestion.¹⁵ Surprisingly, in an experimentally induced storage disorder, axonal dystrophy did not follow neuronal storage but, rather, the two processes developed concurrently.¹⁵

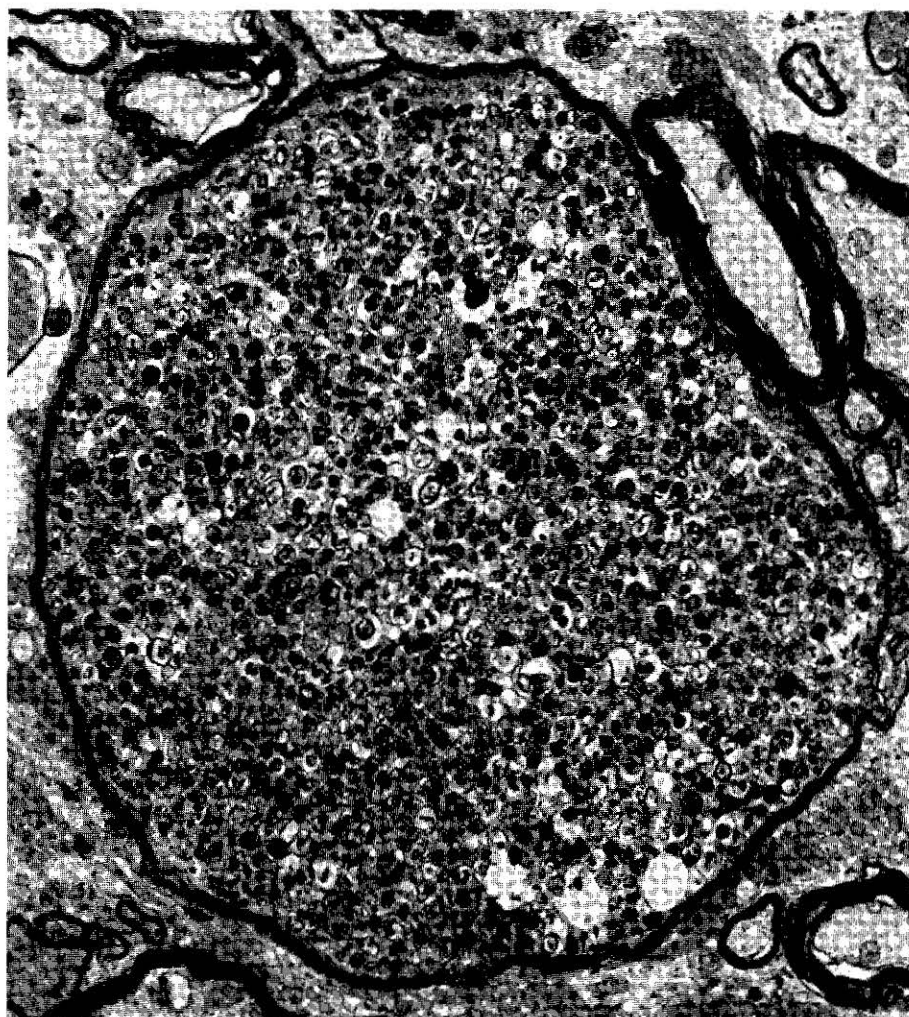


Fig. 5-5. Spheroid filled with electron-dense bodies in gangliosidosis (GM₂), dog. ($\times 6600$.)

The diagnosis of a lysosomal storage disease in animals (and humans) can be made when sufficient evidence has been assembled. In summary, the disorder should be breed-specific, affecting both males and females with an onset early in life with few exceptions. There are signs of a diffuse neurological disturbance with a progressively deteriorating course leading to death. In some cases, the diagnosis can conveniently be substantiated during life by morphological studies of biopsies, for example, in globoid cell leukodystrophy,^{24,25} in which PNS involvement occurs. Characteristically, a positive diagnosis is made postmortem, employing light and electron microscopic morphology, sometimes lectin histochemistry,^{26,27} and biochemistry. Tissue for substrate analysis can be used fresh or else must be snap-frozen; brain, liver, kidney, spleen, and lymph nodes can be sampled, and sometimes urinalysis is informative. The biochemical studies should demonstrate elevated storage of the substrate for which the hydrolase is defective. Some enzymes act on more than one linkage (they are linkage rather

than substrate specific²⁸), and so a range of compounds may accumulate.⁶ Tissue to demonstrate the lysosomal enzyme defect need not necessarily accumulate large quantities of the substrate. Plasma and leukocytes are often valuable for this purpose and are convenient for control programs where many animals are to be tested. Specimens of major organs and cultured cells (usually skin fibroblasts) can also be used.²⁹ If circumstances permit, the breeding can be repeated to substantiate the hereditary basis of the disorder and to establish its pattern of inheritance.

In humans, where antemortem diagnosis is critical, there is a considerable body of literature describing the pathological changes found in blood leukocytes, skin, and other tissue biopsies and in cultured skin fibroblasts.³⁰⁻³² A smattering of comparable published studies exist for the storage diseases of animals, and they are mentioned in this section with each specific disorder. Ultrastructural features of the stored substrate have some diagnostic usefulness, and these structures have acquired their own jargon—membranous

cytoplasmic bodies, zebra bodies, and fingerprint profiles—to name a few.^{31,33} For prenatal diagnosis in humans, cells obtained by amniocentesis can be used. By virtue of the gene dosage phenomenon, levels of the hydrolase in clinically unaffected heterozygotes (which have one normal and one abnormal gene) is approximately 50% that of normal individuals of that species. Control of the syndrome largely centers on heterozygote detection and the elimination of these animals, which perpetuate the disorder, from the breeding pool.³⁴ In practice, identifying individual heterozygotes may be more difficult than this would imply.³⁵

These general comments made, what follows is a review of many of the specific storage diseases that have been reported in animals. This section also includes a short discussion of those novel poisonous plants that in their effects simulate genetic storage diseases. This broad area of veterinary medicine is in constant flux: New storage diseases are being recognized, studied, and characterized, while others, whether single cases or large groups of animals (perhaps maintained as a colony for specific studies), come to be lost, whether through infertility, infection, disinterest, lack of funding, or whatever. The point to be made is that this overview should be viewed as representative of a constantly changing field, rather than all-encompassing.

The early reports of storage diseases in humans and animals attempted to define newly recognized nosological entities in terms of the clinical and pathological features that distinguished the condition. For some of these disorders, the lysosomal deficiency has subsequently been identified. A classical example is bovine α -mannosidosis, for which the initial designation of pseudolipidosis was prudent. In other cases, the nature of the enzyme defect remains more conjectural. Reports continue to appear in which the biochemical defect awaits definition, such as the suspected storage disease that afflicted Hereford calves in Australia.³⁶ Lysosomal storage diseases are probably not confined to domesticated and laboratory animals, as attested to by the disorder described in kangaroos by Rothwell and associates.³⁷ It is curious, however, that there appear to be no reports of inherited lysosomal storage disease in the horse.

Sphingolipidoses

Gangliosidoses

The gangliosidoses are inherited lysosomal storage diseases in which there are defects of ganglioside and oligosaccharide degradation.³⁸ The two major groups are designated **GM₁** and **GM₂ gangliosidosis**. The lysosomal deficiencies in **GM₁** are of acid β -galactosidase, whereas β -hexosaminidase A or B or both, or an activator protein that stimulates hexosaminidase A, are lacking in **GM₂**. In humans, variants within each of these two major groups are recognized: There are infantile (type 1), juvenile (type 2), and adult (type 3) forms of **GM₁**, and variant B (Tay-Sachs), O (Sandhoff), AB, and the rare B1 variant of **GM₂**. Historically these were identified on the basis of the age of

clinical onset and severity of neurological manifestations.⁹ There is now an attempt to define each variant in biochemical terms, such as the deficiency or abnormality of an enzyme subunit.

The gangliosidoses constitute some of the more common lysosomal storage diseases in animals. Some are similar to the variants of **GM₁** and **GM₂** recognized in humans.³⁹⁻⁴¹ The **GM₁** gangliosidosis has been described in **dogs**,^{40,42-44} including **Beagle crossbred**, **English Springer Spaniels**, and **Portuguese water dogs**. It is reported in **cats**,⁴⁵⁻⁴⁷ including **Siamese** and **domestic short hair**, and in **Friesian cattle**.^{35,48} Also **GM₁** gangliosidosis occurs in **Suffolk cross sheep**,⁴⁹⁻⁵¹ in which there is a dual enzyme deficiency. The **GM₂** group has been described in **German Shorthair Pointer dogs**,^{41,52} and the AB variant in a **Japanese Spaniel**,^{53,54} **domestic cats**,^{55,56} and **Yorkshire pigs**.⁵⁷

The clinical features of these diseases are rather similar⁵⁸ and have been compared.⁴⁰ The age at which neurological deficits are reported depends somewhat on the experience and alertness of the owner. Animal breeders, sensitized to a particular disorder, will identify subtle changes early in life. In general, a progressively worsening CNS disorder at approximately 3 to 6 months of age is commonly the reason for consultation. Some animals are noted, at an earlier age, with vague signs such as poor growth rate, depression, and failure to eat. Neurological signs reflect the diffuse nature of the pathological process: there are commonly cerebellar-medullary signs with a dysmetric ataxia and balance loss, basewide stance, intentional type of head tremor, and abnormal nystagmus. Whole-body tremors reflect more diffuse CNS involvement. Sometimes visual deficits are suspected; in some instances, behavioral disorders are reported. Over a few months this kaleidoscope worsens; tetraplegia is often the point at which euthanasia is requested. A tentative diagnosis is supported by the observation of cytoplasmic inclusions in peripheral blood leukocytes, but for disease specificity such would have to be examined ultrastructurally. In some forms of **GM₁** gangliosidosis, oligosaccharides are stored in visceral tissues such as the liver and are excreted in the urine in abnormally high quantities.

Gross pathological changes in the CNS are usually lacking, but the liver may be appreciably swollen and pale. Microscopic study reveals distension of neurons throughout the neuraxis, spinal ganglia, and retina (Fig. 5-6, A). Storage in some somata produces irrefutable cell swelling, typically in the larger neurons such as the pyramidal cells of the cerebral cortex, cerebellar Purkinje neurons, reticular formation, and somatic motor neurons in the ventral horns of the spinal cord. Paraffin sections that are H&E stained reveal a pale, slightly granular quality to the distended perikaryon. Such cells often stain positively in PAS, Sudan Black, and Luxol fast blue stained sections; this is reliable in frozen sections but erratic in paraffin-embedded tissue. Concurrent with the accumulation of storage vacuoles, the nucleus is displaced peripherally and encircled by the re-

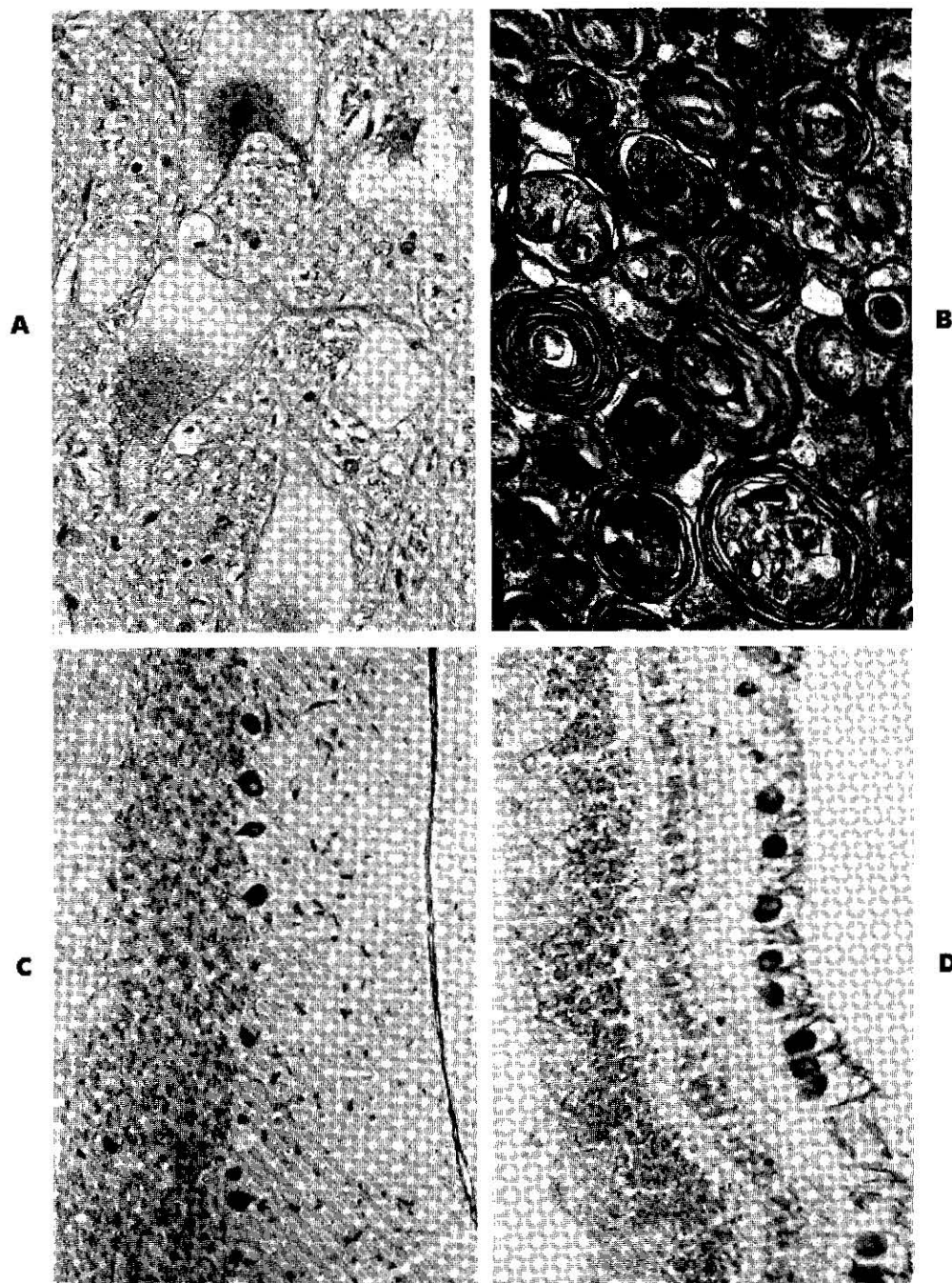


Fig. 5-6. GM₁ gangliosidosis. **A**, Distended neurons in brain stem, cat. (H&E, $\times 350$.) **B**, Membranous cytoplasmic bodies, cat. ($\times 25,000$.) **C**, Lectin (*Dolichos biflorus* agglutinin) stains storage material in Purkinje neurons, calf. ($\times 94$.) **D**, Lectin (*Ulex europaeus* agglutinin-1) staining of retinal ganglion cell layer, dog. ($\times 240$.)

maining Nissl substance in the cell. Degenerate and necrotic neurons are infrequently encountered. A scattering of axonal spheroids may be seen in white matter, and retarded myelin development has been described in canine GM₁ gangliosidosis.⁵⁹ Clear cytoplasmic vacuoles are encountered in other cells, including hepatocytes, Kupffer cells, renal tubular epithelia, pancreatic exocrine cells, and macrophages in lymphoid tissues. Lectin staining of cells with storage material can be performed.

On electron microscopy, neuronal somata are packed with membrane-bound vacuoles containing a membranous, lamellar material. This is commonly seen as concentric whorls (often with a dense amorphous core), and such are referred to as **membranous cytoplasmic bodies** (MCB) (Fig. 5-6, B). In contrast, a tangential section may impart the appearance of stacked, parallel membranes that constitute **zebra bodies**. The MCB consist of alternative lamellae separated by clear spaces, a structure resembling compacted myelin.⁶⁰ Combined Golgi-ultrastructural studies reveal meganeurites (see previous discussion) distended with MCB.⁶¹ Vacuoles may also be found in endothelial cells and pericytes. As in visceral tissues, these membrane-bound vacuoles are usually empty or have only the flocculent or finely granular remnants of oligosaccharides, which have been leached out during tissue fixation. Chromatographic analysis reveals a marked elevation of ganglioside storage, often 5 to 10 times the level of controls. Analysis of lysosomal enzyme activities can often be performed on blood leukocytes or cultured skin fibroblasts. Activity is often only 3% to 5% that of homozygous normals, whereas other hydrolases are preserved, and levels may exceed control values. In the GM₂ AB variant that lacks an activator protein, levels of β -hexosaminidase are actually elevated.⁵³ Levels of microtubule-associated protein (MAP 2), a major component of the neuronal cytoskeleton, was shown to be reduced in GM₁ gangliosidosis of Portuguese water dogs.⁶²

Globoid cell leukodystrophy

Globoid cells—large, globose macrophages—are the hallmark of **globoid cell leukodystrophy** (GCL), a lysosomal disorder that afflicts humans and several animal species. The human variant is also known as **Krabbe's disease**, specifically the common, early infantile form. Myelin of both the CNS and PNS are affected, although the clinical picture is mainly one of a central disorder. Following initial early development until about the fourth month, afflicted infants become irritable, have pyrexia episodes, and develop spasticity and eventually decerebration; death ensues by 1 to 2 years of age. Less frequent are the late infantile⁶³ and juvenile forms of the disorder.

In GCL, which is inherited as an autosomal recessive trait, there is a deficiency of lysosomal **galactosylceramidase 1** (galactocerebroside β -galactosidase), which can be demonstrated by assaying CNS tissue, blood leukocytes, and cultured fibroblasts. The biochemical basis of the disease is complex and challenged investigators to account for

two observations, that is, (1) the failure of galactosylceramide (β -galactocerebroside) to accumulate in the nervous system (as would be expected) and (2) the primary demyelinating nature of the disorder. To address the second point, the **psychosine hypothesis** was proposed in 1972;⁶⁴ this states that psychosine (galactosylsphingosine) is responsible for the myelin destruction in this disease because this lipid, which is highly toxic to oligodendrocytes and Schwann cells, accumulates in GCL. Terminally, elevated brain psychosine levels are perhaps 100 times the norm and have been demonstrated in human, canine, and murine GCL.⁶⁵ Later came a crucial observation—that there are two forms (I and II) of the pivotal enzyme galactosylceramidase.⁶⁶ Galactosylceramide is hydrolyzed by both forms of the enzyme and hence continues to be metabolized, whereas psychosine, which accumulates, is degraded by only galactosylceramidase I, the deficient hydrolase.⁶⁷

The first account of GCL in animals was probably the report by Fankhauser, Luginbühl, and Hartley in 1963.⁶⁸ In the **dog**, GCL is most commonly recognized in West Highland White⁶⁹ and Cairn^{70,71} terriers, in which breeds an autosomal recessive mode of inheritance is established. There are reports of single cases in other canine breeds including a Pomeranian,⁷² a Basset hound,⁷³ a possible case in a Miniature Poodle,⁷⁴ and three affected male Bluetick hound dogs are described.⁷⁵ Clinical signs appear multifocal and begin at about 3 to 5 months of age, often with complaints that affected dogs seem to be ataxic and fall repeatedly on their pelvic limbs. Frequently there is also a tremor of the head or a generalized tremor that is associated with activity (intentional). Spinal deficits are progressive over a course of several weeks, leading to paraplegia with loss of patellar reflexes, a sign of PNS involvement. Thoracic limbs are usually more mildly involved with spasticity and hypermetria. Muscle wasting is commonly noted. Terminally, tetraplegia as well as blindness and dementia have been observed, usually prior to 1 year of age.

Examination of CSF reveals an albuminocytologic dissociation, that is, increased protein without a concurrent pleocytosis. However, careful examination of CSF from affected West Highland White terriers has shown the presence of PAS-positive mononucleated or multinucleated globoid cells.⁷⁶ Because canine GCL consistently affects the PNS,⁷⁷ ultrastructural examination of a nerve biopsy may aid in reaching a diagnosis,^{24,25} and diminished conduction velocity in peripheral nerve has been recorded.⁷² The case in the Basset is of interest as the animal became ataxic at 4 years of age. Pathological changes were characteristic in type but atypical in distribution, being limited to the brain stem and spinal cord. Clinically, globoid cell leukodystrophy and the diffuse neuronal chromatolytic disease (see the section on abiotrophies) in the Cairn terrier may be confused.

At necropsy, the intact brain appears normal, but there is grayish discoloration and firmness of cerebral and, to some degree, cerebellar white matter. The ventricles are

mildly to markedly dilated, reflecting tissue (white matter) loss. White matter lesions are bilaterally symmetrical but vary in severity within the neuraxis and from case to case. The centrum semiovale, corona radiata, corpus callosum, optic tract, and cerebellar medulla are most markedly affected. Within the spinal cord, peripheral subpial zones are characteristically the site of lesions. Histological examination is remarkable for a combination of myelin pallor and hypercellularity, the latter due to the striking perivascular accumulation of globoid cells and a reactive astrocytosis in the tissue. A few globoid cells are found within the white matter parenchyma, and some will be noted in the leptomeninges. In developed lesions, the white matter stains weakly with myelin stains compared to unaffected areas, and oligodendrocyte numbers are reduced.⁶⁹ In human cases of GCL, sparing of the myelinated fibers at the junction of the cerebral cortex and the corona radiata (association U fibers) is often emphasized but has less commonly been noted in the dog.⁷¹ In advanced, more porotic lesions, there is axonal swelling, fragmentation, and necrosis, and eventually globoid cells are less plentiful. Within the peripheral nerves, there is separation of myelinated fibers by globoid macrophages; segmental demyelination, particularly of larger-diameter axons; and some axonal degeneration.

The **globoid cells** are round to oval, single or multinucleated macrophages with central roundish or eccentric flattened nuclei and vacuolar to granular cytoplasm (Fig. 5-7). These cells are PAS-positive and nonmetachromatic, and in paraffin sections they can be stained with several lectins, most consistently succinylated wheat germ.⁷⁸ A scattering of lymphocytes and plasma cells percolate among them. Characteristic of GCL is the absence of the conventional, lipid-laden macrophages (gitter cells) that would normally accompany a demyelinating or necrotizing white matter disorder; instead, globoid cells form. Although galactosylceramide does not appreciably accumulate in this condition, myelin-forming cells contain galactosylceramide inclusions, as do the macrophages in areas of white matter degeneration. In fact, the formation of globoid cells can be induced by the intracerebral injection of this sphingolipid.⁷⁹

The ultrastructural features of the canine globoid cell have been described by several authors.^{24,25,73,80,81} Cytoplasmic contents are an admixture of intact and partially degraded myelin membranes and the diagnostic membrane-bound aggregates of straight, arched, and twisted tubules of galactosylceramide (Fig. 5-8). Inclusions are found also in oligodendrocytes and Schwann cells. Deficiency of galactosylceramidase has been demonstrated in the brain, liver, and kidney of affected dogs.⁸²

Globoid cell leukodystrophy has been described in inbred **domestic shorthaired cats**⁸³ and in two polled **Dorset sheep**.⁸⁴ In the affected sheep, galactosylceramidase activity was only 6% that of the controls. The **mouse mutant twitcher** is an important laboratory model of human GCL.^{85,86} Affected mice are normal until about 3 to 4 weeks, at which age they begin to lose weight, develop a tremor

and an ataxic gait, and are paraparetic. Death is common by 5 to 7 weeks. Degeneration of spinal cord myelin begins from about 20 to 25 days of age⁸⁷ and even earlier in the PNS,⁸⁸ and fine structural changes in oligodendrocytes and their myelin sheaths have been described.^{79,89} Failure of normal myelination (hypomyelination) and myelin degeneration correlate well with the increasing concentrations of psychosine. Transplantation of bone marrow cells alone⁹⁰ or in combination with spleen cells⁹¹ into homozygous twitcher mice resulted in prolonged survival, improved locomotor ability, remyelination in the PNS and CNS, and a progressive replacement of CNS globoid cells with normal, enzymatically competent, donor-derived macrophages. Psychosine levels were diminished but despite morphological improvement in the CNS of mice that survived beyond 100 days, oligodendrocytes still contained galactosylceramide inclusions.⁹²

Metachromatic leukodystrophy

Metachromatic leukodystrophy (MLD) in humans is caused by an inherited deficiency of the lysosomal enzyme **arylsulfatase A** or its activator protein.¹ Late infantile, juvenile, and adult-onset forms are recognized, the first being most common. The accumulation of metachromatic products of degenerate myelin in these patients was the feature originally employed to define the disorder in pathological terms, just as the presence of globoid cells characterizes Krabbe's disease. We now know that these two leukodystrophies are lysosomal disorders.

Diseases of the nervous system in animals that are entirely comparable to human MLD have not been recorded, as in none was the underlying enzymatic defect established. An apparently inherited, progressive neurological disorder of **mink** was seen in Denmark in the 1960s. Animals were affected between 40 and 150 days of age⁹³ with tremor, particularly of the head; balance loss; and paraparesis that progressed to paraplegia. Pathological changes were found diffusely throughout the white substance of the CNS, with degeneration of myelin, astrocytosis, and the accumulation of granular material extracellularly and within cells (often perivascular arrangement), which stained metachromatically with toluidine blue and cresyl violet.⁹⁴ Wight⁹⁵ reported a lipidosis in two **Hawaiian geese**; it involved neuronal populations, central white matter, and peripheral nerves. Metachromatic material was found in neurons and perivascular macrophages and sulfatide levels in the white matter were elevated. Finally, a brief abstract⁹⁶ records a diffuse demyelinating disease of kittens with PAS and metachromatic inclusions in glial cells in the white matter.

Gaucher's disease

Gaucher's disease is the most common human sphingolipidosis, resulting from a deficiency of the lysosomal enzyme **glucocerebrosidase** (glucocerebrosidase β -glucosidase) that catalyzes the hydrolysis of glucocerebroside,

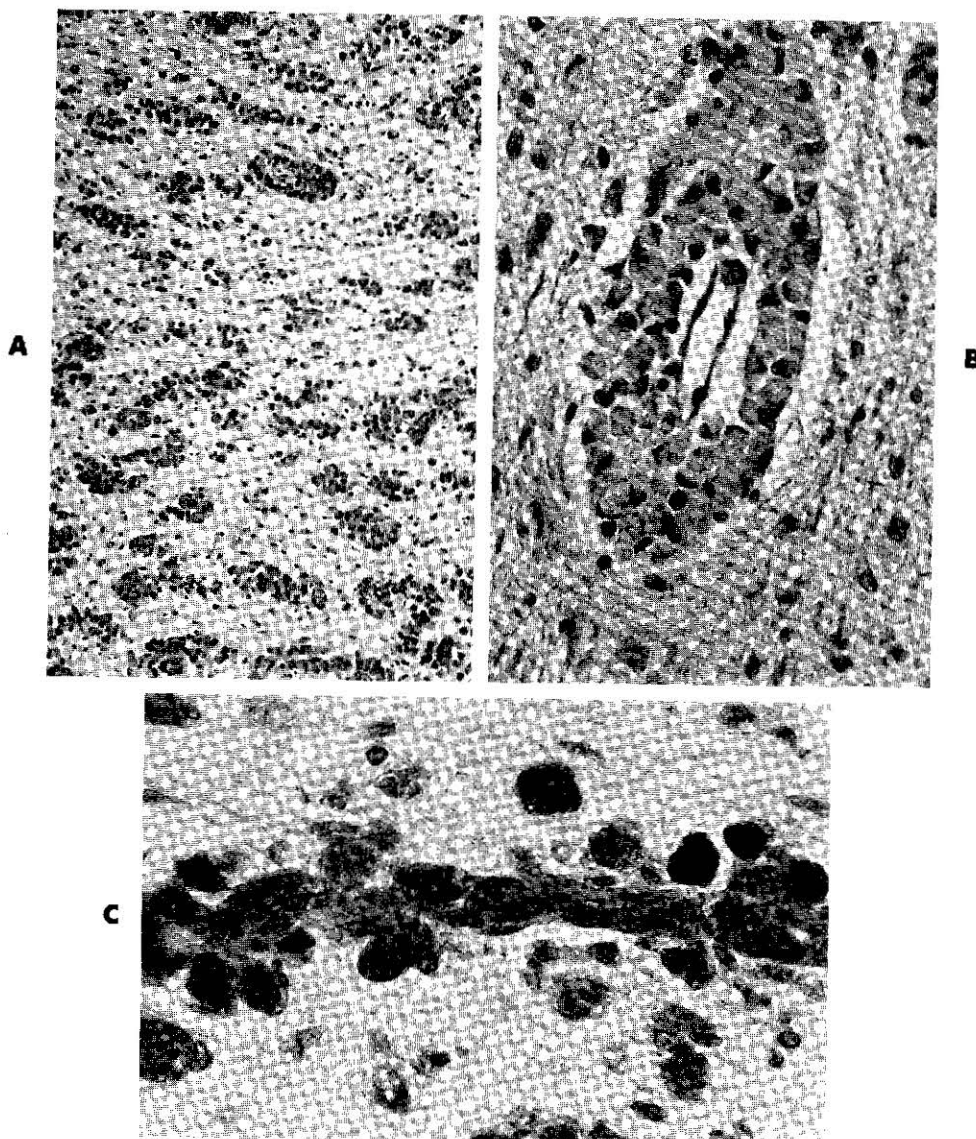


Fig. 5-7. Globoid cell leukodystrophy, dog. **A**, Cerebral white matter. Blood vessels are cuffed by globoid cells. (PAS, $\times 140$.) **B**, Detail of perivascular globoid macrophages. (H&E, $\times 560$.) **C**, Lectin (succinylated wheat germ agglutinin) stained globoid cells. ($\times 560$.)

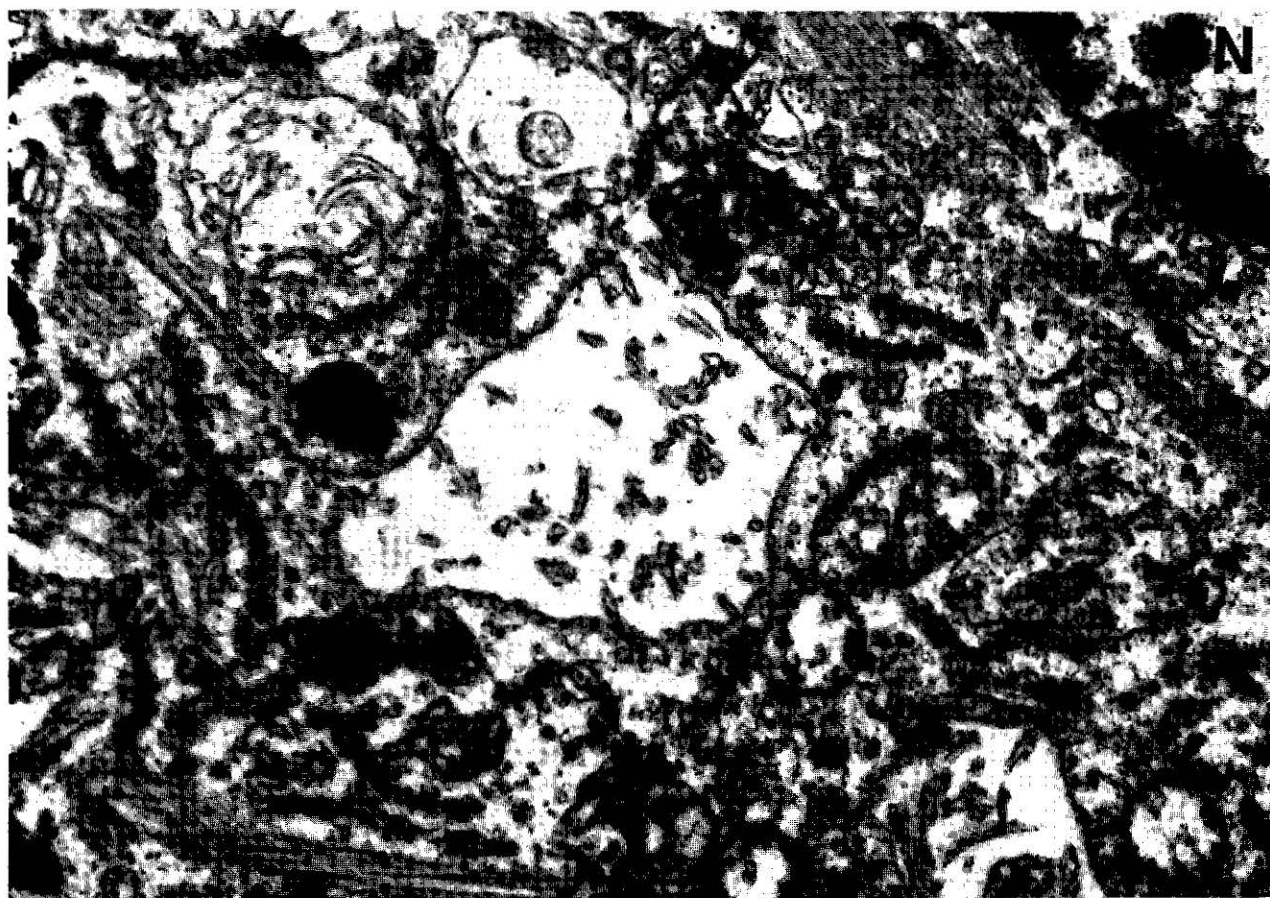


Fig. 5-8. Globoid cell leukodystrophy. Ultrastructural detail of the cytoplasmic inclusions, which consist of variably sized straight and curved tubular profiles. N is nucleus of the macrophage. ($\times 24,250$.)

yielding ceramide and glucose.^{1,97} Glucocerebroside accumulates in lysosomes, particularly in macrophages in the liver, spleen, and bone marrow and sometimes in neurons. The most common form of human Gaucher's disease (type 1, adult) is relatively benign with a chronic course of hepatosplenomegaly and myelophthitic pancytopenia. More fulminating is the type 2, infantile, neuronopathic form, which is usually lethal before 2 years of age. There is also a juvenile, subacute, neuronopathic form (type 3), usually progressing to death in early adulthood. Studies are underway in an attempt to understand the basis for these phenotypic variations.⁹⁷

A few **Australian (Sydney) Silky terrier dogs** with a form of Gaucher's disease similar to human type 2 have been studied.^{98,99} Presentation at about 4 months of age is one of slowly worsening cerebellar ataxia, tremor, and hyperactivity. Grossly the brain and spinal cord are unremarkable, but microscopically many neurons are distended and have a vacuolated, foamy, or granular cytoplasm. Thalamic and hippocampal neurons are most strikingly affected, but others in the cerebral cortex and brain stem are also involved. Degeneration and necrosis of individual neurons

or groups of neurons are also encountered in the cerebral and cerebellar cortices (the latter in granule and Purkinje cell neurons) and the dorsal nuclei of the trapezoid body in the medulla. Characteristic foamy, distended macrophages (Gaucher cells) infiltrate the cerebellar granule cell layer and are found also in lymph nodes and liver. Myelin spongiosis affects the cerebral and spinal cord white matter and, at least in part, indicates Wallerian degeneration. Ultrastructurally, the storage cytosomes in neurons contain membranous laminae resembling zebra bodies admixed with a delicate, wispy material. Gaucher cells contain twisted tubules, but their observation in neurons is rare.⁹⁹ There is elevated storage of glucocerebroside, particularly in the liver, and at pH 4 to 4.25 (but not at a higher pH) a deficiency of tissue β -glucosidase activity.¹⁰⁰

Niemann-Pick disease

Niemann-Pick disease (sphingomyelin lipidosis) is a lysosomal storage disorder that results in the neurovisceral accumulation of sphingomyelin, cholesterol, and glycosphingolipids such as ganglioside GM₂ and GM₃.¹ In **humans**, six clinicopathologically distinct variants of Nie-

mann-Pick disease are recognized and designated types A to F.^{101,102} There are differences between the human phenotypes in the extent of storage in neural and visceral tissues (liver, spleen) and in the clinical course: Type A is acute and neuropathic, whereas type B is chronic and nonneuropathic. The biochemical bases for some types of this disorder remain to be fully clarified. In types A and B, there is severe (even total) deficiency of **acid sphingomyelinase** activity, whereas patients with types C and D have only partial or no reduction in the activity of this enzyme. If sphingomyelinase deficiency is the underlying defect in Niemann-Pick disease, why other lipids that are not substrates of this enzyme accumulate is not known.¹

Storage disorders in animals comparable to Niemann-Pick disease have been recognized mainly in cats and mice. **Feline** cases include Siamese,¹⁰²⁻¹⁰⁵ Balinese,¹⁰⁶ and domestic^{107,108} cats with diverse clinical and pathological features. Some have resembled Niemann-Pick disease type A, with presentation in the first months of life for a progressive disorder manifest as balance loss, head tremors, paraparesis, weight loss, and depression. At necropsy, there is hepatomegaly with a yellow, swollen liver. Light microscopic examination reveals cytoplasmic vacuolation of hepatocytes; renal tubular epithelia (in the cat some vacuolation is normal in the proximal tubule); macrophages in bone marrow, lung, spleen, lymph nodes, and the neurons and glia of the brain and spinal cord.¹⁰⁵ Not all neurons in the CNS are equally affected by inclusions, and they vary from clear vacuoles to finely granular eosinophilic aggregates that displace the nucleus. Ganglion cells in the retina, cranio-spinal ganglia, and myenteric plexus are similarly affected. Some authors have found that in PAS-stained frozen sections neuronal cytosomes do not stain, while cerebrovascular endothelial and pericytic inclusions are strongly positive;¹⁰⁶ others¹⁰⁴ have had the opposite results. Spheroids are common throughout the brain,¹⁰⁷ as many pathologists have observed in lysosomal storage diseases. In the Siamese cat, Con A lectin stains diverse populations of neurons with storage material.¹⁰⁹

Ultrastructural examination of the CNS in affected cats reveals a variety of membrane-bound cytosomic profiles. Some are membranous and concentrically arranged, qualifying as membranous cytoplasmic bodies; others (perhaps tangentially sectioned) have the stacked organization of zebra bodies. Other storage inclusions have mixed membranous and vacuolar features.¹⁰⁶ Inclusions are found also in glial cells, endothelia, and pericytes. In contrast, the structures segregated within swollen axons are predominantly amorphous dense bodies, mitochondria and some membranous profiles.

Analysis of liver, brain, and blood leukocytes reveals a lack of acidic sphingomyelinase activity (nonlysosomal, Mg + + -dependent sphingomyelinase activity at neutral pH is unaffected), and these tissues have excessive storage of sphingomyelin, cholesterol, and gangliosides.^{103,106} Cuddon

and colleagues¹⁰² have reported three 4- to 7-month-old cats with Niemann-Pick disease that on clinical presentation (flaccid tetraparesis, hypotonia, hyporeflexia), electrodiagnostic studies, and muscle biopsy had the features of a demyelinating polyneuropathy. Despite these clinical signs, there was marked lysosomal storage in the CNS, while the peripheral nerves were marked by demyelination, axonal preservation, and remyelination. Measurement of acid sphingomyelinase activity and analysis of storage materials suggested type A Niemann-Pick disease in one cat and variants of this in the other two.

We have observed a storage disorder resembling Niemann-Pick disease type C in the domestic cat.¹⁰⁸ Storage was found in visceral organs and in the CNS, spinal, and enteric ganglia. As in this human phenotype, neuroaxonal dystrophy was pronounced, particularly in cerebral, cerebellar, and spinal cord white matter, in cerebellar nuclei, and in the granule cell layer of the cerebellar cortex. In further accord with this variant, sphingomyelinase activity was only mildly depressed, whereas the capacity of cultured skin fibroblasts to esterify cholesterol was markedly subnormal.

Reports of Niemann-Pick disease in the canine species (Fig. 5-9) are rare. Neurovisceral storage of sphingomyelin and cholesterol with no sphingomyelinase activity in the brain has been described in a 5-month-old **miniature Poodle dog**.¹¹⁰ A few storage disorders have been identified in **mice**, which to varying degrees are comparable to Niemann-Pick types A, B, or C.¹¹¹⁻¹¹³ In the C57BL/KsJ mutant strain¹⁰¹ early hepatosplenomegaly precedes the development of a progressively severe ataxia, tremor, and wasting. In these mice, there is marked cerebellar atrophy with severe depletion of Purkinje cells.

Glycoproteinoses

Fucosidosis

Fucosidosis is a lysosomal storage disease resulting from **α -L-fucosidase** deficiency, which leads to the accumulation of fucoglycoproteins, oligosaccharides, and glycosaminoglycans.¹ There is neurological and visceral involvement, and **infantile** and **juvenile** patterns are recognized in humans. The disorder in animals occurs in **English Springer Spaniel dogs**, and those cases recognized in England and Australia have a common ancestor.¹¹⁴ The malady is evident from about 12 months of age and progresses to demise within 2 to 3 years. The first manifestations are behavioral changes—difficulty in handling and training, loss of learned commands—and are soon followed by changes in the gait with proprioceptive deficits and ataxia.^{115,116} Sight and hearing progressively decline, the animals lose weight, and (characteristically) the bark becomes hoarse. Dysphagia is seen in some cases, and occasional animals develop bronchopneumonia, presumably from aspiration. Enlargement of certain peripheral nerves is a hallmark of the canine disorder, and ulnar nerve swelling is palpable in advanced

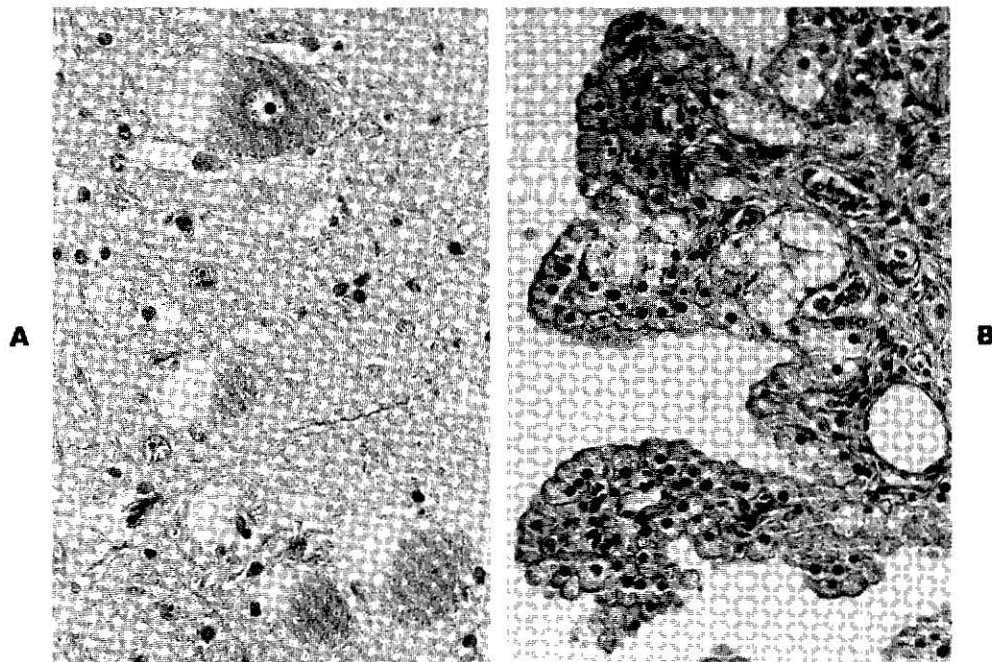


Fig. 5-9. Niemann-Pick disease, dog. **A**, Storage vacuoles in neurons of mesencephalic V. (H&E, $\times 360$.) **B**, Cytoplasmic pallor of choroid plexus epithelium due to storage material. (H&E, $\times 360$.)

disease.¹¹⁴ Storage vacuoles can be found in peripheral blood lymphocytes, CSF and bone marrow macrophages,¹¹⁴ and markedly depressed levels of α -L-fucosidase are found in plasma, CSF, and tissues^{114,117} and cultured fibroblasts.¹¹⁸ An autosomal recessive mode of inheritance is proposed.¹¹⁷

At necropsy, the remarkable gross changes in the nervous system are in peripheral nerves and their associated ganglia. There is thickening of the vagus nerve, spinal nerves of the cervical intumescence that contribute to the brachial plexus, and hypoglossal, glossopharyngeal, and intercostal nerves.^{115,118} Affected nerves are swollen, grayish, and very firm. The associated spinal ganglia are appreciably enlarged also. This selective involvement of certain peripheral nerves and their sensory ganglia is a strange peculiarity of the canine disease that is unexplained.

Microscopic study reveals severe and widespread cytoplasmic vacuolation of neurons and neuroglia throughout the brain (Fig. 5-10) and more cranial spinal cord. Somata of neurons have fine, foamy vacuolation that may harbor PAS-positive granules. Replacement of Nissl aggregates varies from mild to total. In some areas, such as the cerebellar Purkinje cells and the cuneate and gracile nuclei, neurons are lost. Macrophages with prominent, clear vacuoles are found in perivascular and leptomeningeal spaces and within the neuropil (microglia). Other glial cells have pronounced cytoplasmic vacuoles and pyknotic nuclei and are often difficult to identify other than by site, such as neuronal satellite cells. Dystrophic axons are found randomly but particularly in hypothalamic, cerebellar, cuneate, and gracile nuclei and are accompanied by hypertrophic

astrocytes. Evidence of Wallerian degeneration is found in cerebral, cerebellar, and spinal cord white matter. Storage vacuoles in the human disease bind Con A and Ulex europeus-1 lectins.²⁶

Changes accounting for the remarkable hypertrophy of the proximal portions of cranial and spinal nerves are edema, fibroplasia, and aggregation of chains of vacuolated macrophages between nerve fibers within the fascicles. Macrophages collect within the endoneurium. Surviving myelinated fibers are separated by the loose matrix, but evidence of active degeneration is not pronounced, and denervation atrophy of dependent musculature is not a feature of the disease. In sensory ganglia, neurons and satellite cells have vacuolated cytoplasm and fibroedematous change. Cell bodies of the enteric ganglia are affected. Macrophages in lymphoid organs resemble those of nervous tissues, and epithelia of pancreatic, biliary, renal, and other organs have storage also. The substrate that accumulates appears to be soluble, as ultrastructurally the cytosomes in the neuraxis and in phagocytic cells are largely empty, save for a little amorphous debris. Straight to curved, lamellar membranous deposits occur in some neuronal somata.

Based on plasma or leukocyte α -L-fucosidase activity, a trial to identify carrier heterozygous English Springer Spaniels was initiated in England¹¹⁹ but has shown that there is an overlap in the levels between heterozygous and normal dogs. In contrast, in affected animals, activity is less than 2% of the norm.¹²⁰ Farrow¹²¹ has explored the feasibility of allogeneic bone marrow transplantation as a therapeutic option for this lysosomal storage disease, with encouraging

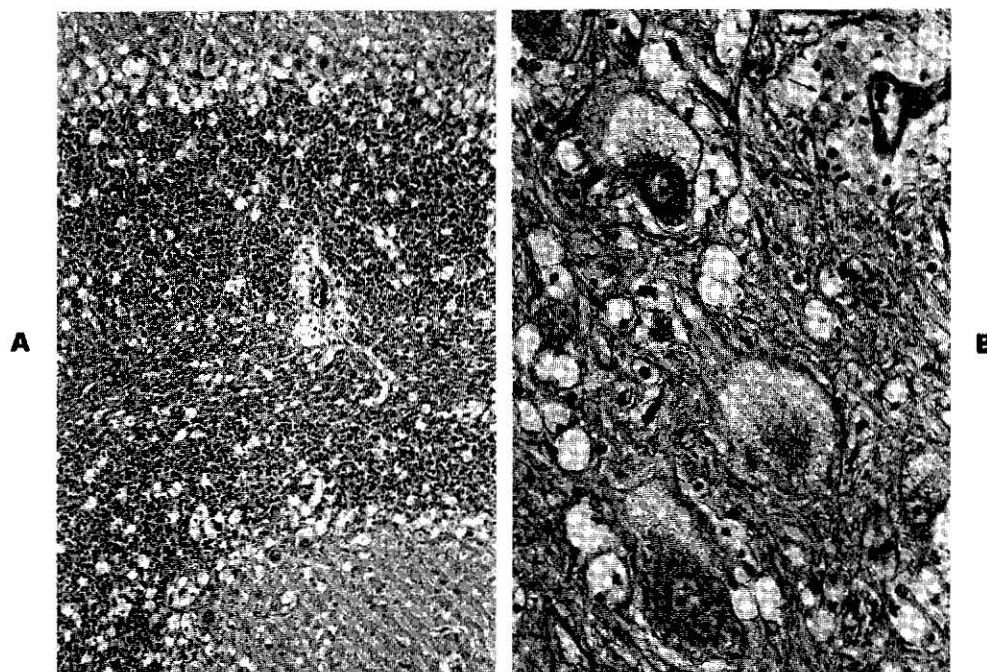


Fig. 5-10. Fucosidosis, dog. **A**, Vacuolar storage in glial cells, cerebellum. (H&E, $\times 140$.) **B**, Cerebellar nucleus showing neuronal and glial storage vacuoles. Perivascular macrophages (arrow) are characteristic. (H&E, $\times 350$.)

results. The further possibility of correcting the enzymatic deficiency by retroviral-mediated gene transfer into hematopoietic progenitor cells of human Gaucher disease patients has also been examined.¹²²

Mannosidosis

Mannosidosis is the syndrome associated with a deficiency of lysosomal acidic α - or β -mannosidase, resulting in storage of glycoprotein-derived, mannose-rich oligosaccharides. Human α -mannosidosis is recognized but is uncommon. Affected patients have coarse facial features, ataxia, and mental retardation. In the type II phenotype, there is longer life expectancy than is the case for many other lysosomal storage diseases. Type I patients deteriorate rapidly, usually by their tenth year. Clear storage vacuoles are found in macrophage populations, blood leukocytes, endothelia, fibroblasts, epithelial cells, and neurons of the CNS, retina, and enteric ganglia.¹²³ Mannose-containing oligosaccharides are stored in these lysosomal compartments, which ultrastructurally are largely empty or harbor but fluffy remnants of the water-soluble substrate. Levels of α -mannosidase in leukocytes or cultured skin fibroblasts are below 5% of controls. Lectin histochemistry may assist in identifying the stored substrate.²⁶ Human β -mannosidosis is even more exceptional, the first case identified being reported in 1986.¹²⁴

In contrast to its low prevalence in humans, α -mannosidosis is (or was) common and qualified as a disease of economic importance in **Aberdeen Angus cattle**. It is also

recorded in the **Murray Grey**¹²⁵ and **Galloway**¹²⁶ breeds. Originally studied in Australia and New Zealand, it has since been recorded in the United States, England,¹²⁷ and possibly South Africa.¹²⁸ There is variation in the phenotypic expression of the disorder in cattle both within and between breeds.¹²⁹ Some affected Angus calves are born prematurely and die soon after, and this seems to be the common pattern in Galloways. Some Angus calves are born at full term but are dull and lethargic and have severe cerebellar ataxia. In others, signs of CNS disease are recognized within the first year of life, often by 6 months, but occasionally not until 15 months of age. The original description by Whittem and Walker in 1957¹³⁰ reported a progressive neurological disease in calves characterized by truncal ataxia, head tremor, hypermetria, and sometimes aggressive behavior. Death by 18 months is common.

At necropsy, affected calves are usually poorly grown and have lymphadenopathy. The ventricular system of the brain is mildly to moderately dilated. Maxillary brachygnathia and hepatorenomegaly have been recorded.^{126,129} Microscopic findings are of variably severe cytoplasmic vacuolation of neurons and neuroglia, macrophages, fibroblasts, vascular endothelia, pericytes, and epithelial cells of exocrine glands (e.g., pancreas, lacrimal, and salivary). Within the CNS, cytomegaly with cytoplasmic vacuoles is most conspicuous in cerebellar Purkinje cells, the parasympathetic nucleus of the vagus, the hypoglossal nucleus, and spinal somatic motor neurons.¹³¹ In paraffin-embedded tissues, neuronal vacuolation is not always readily appreciated

and is shown to better effect in 1-micrometer sections from plastic. Spheroids, well demonstrated by silver impregnation techniques, are conspicuous in gray and white matter, especially in the Purkinje cell axons and the gracile and cuneate nuclei. A modest degree of hypomyelination (cerebellum and cerebrum) is found. Central nervous system lesions have been found in 6- to 8-month-old fetuses.¹³² Ultrastructurally, the lysosomal storage vacuoles are typically depleted of their storage material (because of its solubility) with occasional granular or membranous remnants. Spheroids are found within myelinated and unmyelinated axons. Lipofuscin granules are of increased prominence in the processes of glia in affected calves. Schwann cells are vacuolated but PNS myelin is intact.¹³²

Tissue α -mannosidase is depleted particularly in the Galloway calves, which seem to be very severely affected. As is often found, other lysosomal enzyme activities are elevated. Hocking, Jolly, and Batt defined the enzymatic defect¹³³ and organized a program to identify carrier heterozygous Angus cattle by measuring plasma α -mannosidase activity.^{134,135} The disorder has autosomal recessive inheritance.

Feline α -mannosidosis has been recorded by several investigators in the **Persian** breed and in a few **domestic breeds**. Some cases have occurred in the progeny of brother-sister matings. As with the disorder in cattle (and humans), there is a clinical and pathological spectrum.¹³⁶ In the Persian kittens described by Vandeveld and associates,¹³⁷ stillbirth and neonatal mortality were recorded; other kittens were affected such that they succumbed or were sacrificed by 3 months of age. Other Persian cats^{138,139} have had a slightly more protracted course, and the cases in domestic short-¹⁴⁰ or long-haired cats¹³⁶ even more so. Clinical presentation consists of skeletal abnormalities and neurological signs, including an ataxic-dysmetric gait and head tremor. In some, a palpably enlarged liver has been noted, and gingival hyperplasia is recorded,¹³⁸ a finding in the human disease. Vacuolation is evident within the cytoplasm of lymphocytes and monocytes in Giemsa-stained blood smears,^{139,141} and ultrastructural examination reveals milder changes in other leukocytes. Excretion of oligosaccharides in the urine is heightened. At necropsy, a variety of gross abnormalities may be encountered, including hepatomegaly, lymphadenopathy, skeletal deformity, and thymic aplasia. Microscopically there is cytoplasmic vacuolation of CNS neurons, particularly in the brain stem, cerebellar Purkinje cells, and the ventral horn of the spinal cord. Purkinje cell involvement may progress to degeneration and loss.¹³⁶ There is milder involvement of astrocytes and oligodendrocytes, but vacuolation of parenchymal and perivascular brain macrophages is conspicuous.¹⁴⁰ The lectin concanavalin A will demonstrate the oligosaccharide storage (Fig. 5-11). Vascular endothelial cells and pericytes are affected, as shown by fine structural study. Several authors have identified hypomyelinogenesis^{137,138} of cerebral and/or cerebellar

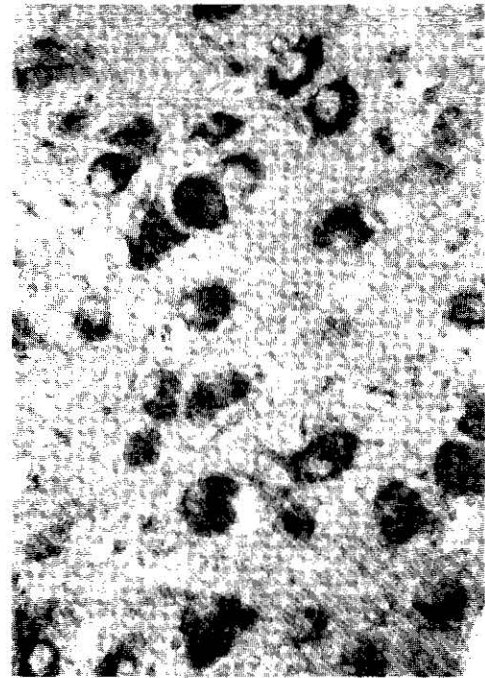


Fig. 5-11. Alpha-mannosidosis, cat. Lectin (Concanavalin A) staining of thalamic neurons. ($\times 240$.)

white matter. Such has been noted also in bovine α -mannosidosis, is conspicuous in animals with β -mannosidosis, and is of uncertain pathogenesis. Widespread axonal spheroid formation is common. Vacuolated macrophages have been found within peripheral nerves.¹⁴⁰ Cytoplasmic vacuolation is found also in hepatocytes, pancreatic exocrine cells, salivary glands, and other tissues. Ultrastructural findings vary from empty cytosomes to wispy, lamellar profiles to whorls reminiscent of membranous cytoplasmic bodies. Lipofuscin granules may also be encountered.¹³⁶ Tissue analyses reveal severe α -mannosidase deficiency¹⁴² and approximately 50% activity in heterozygotes. Abnormalities in neuronal geometry, found in a range of lysosomal storage disorders, have been demonstrated in feline α -mannosidosis.¹⁴³

In Australia, the United States, and perhaps elsewhere, a number of **toxic plants** induce neurological disorders in animals that graze on them. The Australian plants are members of the genus *Swainsona*, and they contain an indolizidine alkaloid which has been named swainsonine. The North American plants are members of the genera *Astragalus* and *Oxytropis*, which may be one and the same. Some of the American plants are nontoxic; some are toxic by virtue of their nitro-compounds, others by accumulating selenium, and yet others by producing CNS disease (hence designated, locoweeds).¹⁴⁴ In sheep, cattle, and horses that consume these plants, a disorder ensues characterized by a stumbling, staggering gait, truncal ataxia, muscle tremors, blindness, and progressive dullness and wasting.^{145,146} The pathological

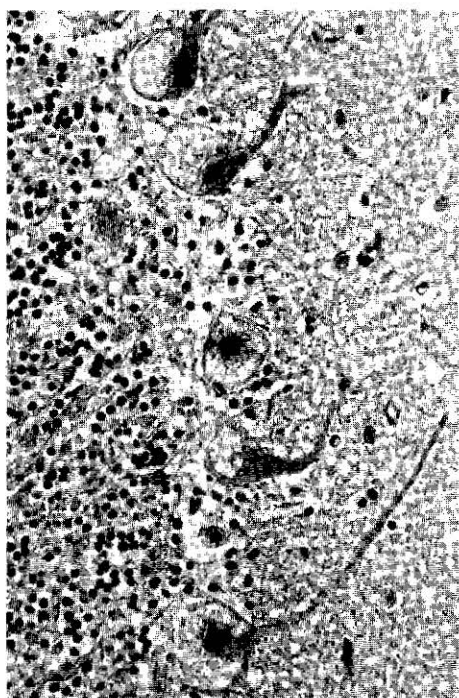


Fig. 5-12. Locoweed poisoning, sheep. Vacuolation of Purkinje cells. (H&E, $\times 350$.)

findings are of neurovisceral lysosomal storage (Fig. 5-12) that mimics that of mannosidosis, and, indeed, these plants contain potent inhibitors of α -mannosidase enzyme,¹⁴⁷ a curious evolutionary development. The pathological effects of *Astragalus* and *Swainsona* are very similar,¹⁴⁸ and the pattern of lectin binding in tissues from animals with genetic α -mannosidosis or with *Astragalus* and *Swainsona* toxicosis is the same.¹⁴⁹

Consumption of these plants for only a few weeks induces changes that are reversible with removal from the source. Studies with swainsonine intoxication in sheep have shown clearance of storage cytosomes within 10 days, and most structural alterations (cytoplasmic vacuoles and neuronal meganeurites) are largely reversed.¹⁵⁰ Some dystrophic axonal swellings may persist. Ingestion of these plants by pregnant animals can induce fetal mannosidosis.^{151,152}

A lysosomal storage disorder of **Nubian goats**, which proved to be **β -mannosidosis**, was first reported by Hartley and Blakemore in 1973.¹⁵³ These animals (both males and females) are affected from birth with prominent neurological and skeletal abnormalities. They lie recumbent and are unable to rise, but are bright and alert. Further, they have a marked tremor that worsens with effort, ocular movements that resemble pendular nystagmus, and are deaf. Facial dysmorphism is exhibited by narrowed palpebral fissures, a domed skull with a sunken nasal bridge, and an elongated muzzle. Each carpus is fixed in flexion, the forelimb pasterns in extension and the pelvic limbs are hyperextended. Affected goat kids are viable for only a few weeks.

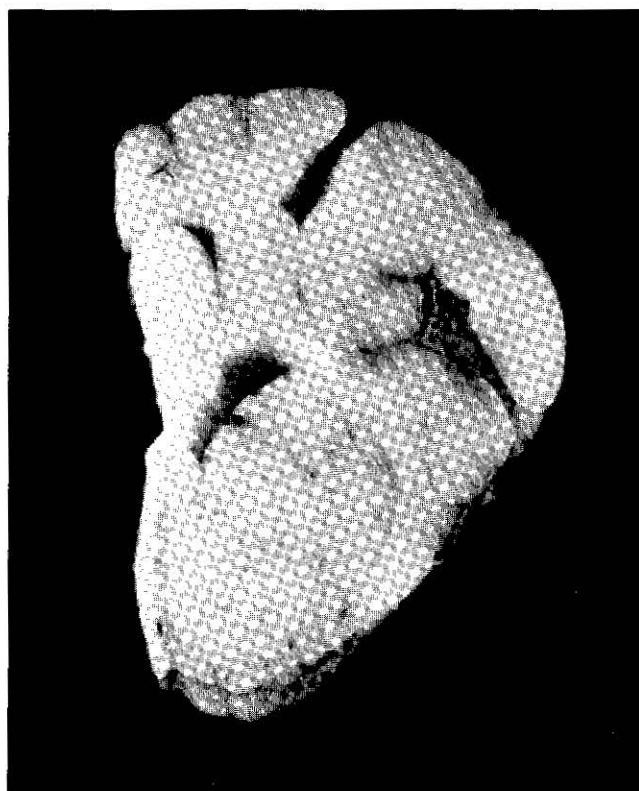


Fig. 5-13. Beta-mannosidosis, goat. Hypomyelinogenesis, cerebrum.

At necropsy, the sectioned brain reveals ventricular dilation and grayish pallor of the cerebral and cerebellar white matter (Fig. 5-13). Microscopically, cytoplasmic vacuolation is the most remarkable finding (Fig. 5-14, A) and affects virtually all neuronal populations and glial cells.¹⁵⁴ Neuronal vacuolation is most severe in cerebrocortical populations, which are ballooned, Nissl bodies are diminished, and the nucleus is displaced to the cell margin. Cytoplasmic vacuolation also affects astroglia, oligodendroglia, the choroid plexus epithelium, vascular endothelia, pericytes, and fibroblasts. Neurons in the craniospinal ganglia, retina, and Schwann cells in the PNS are vacuolated, as are macrophages in lymphoid organs and parenchymal cells of the liver, kidney, pancreas, and other organs.¹⁵⁴ The white matter contains a scattering of axonal spheroids, a common observation in storage diseases.

Histologically, myelin deficits are somewhat more widespread than a gross appraisal would suggest, and this hypomyelinogenesis probably accounts for the congenital tremor. Myelin deficiency is most severe in the corpus callosum, rostral commissure, and internal capsule; areas of the centrum semiovale, optic chiasm, optic tract, and caudal commissure have the least myelin reduction.¹⁵⁵ In areas lacking myelin, oligodendrocyte numbers are reduced, and this is also observed in vitro if oligodendrocyte cultures are established from the brains of affected goat kids.¹⁵⁶

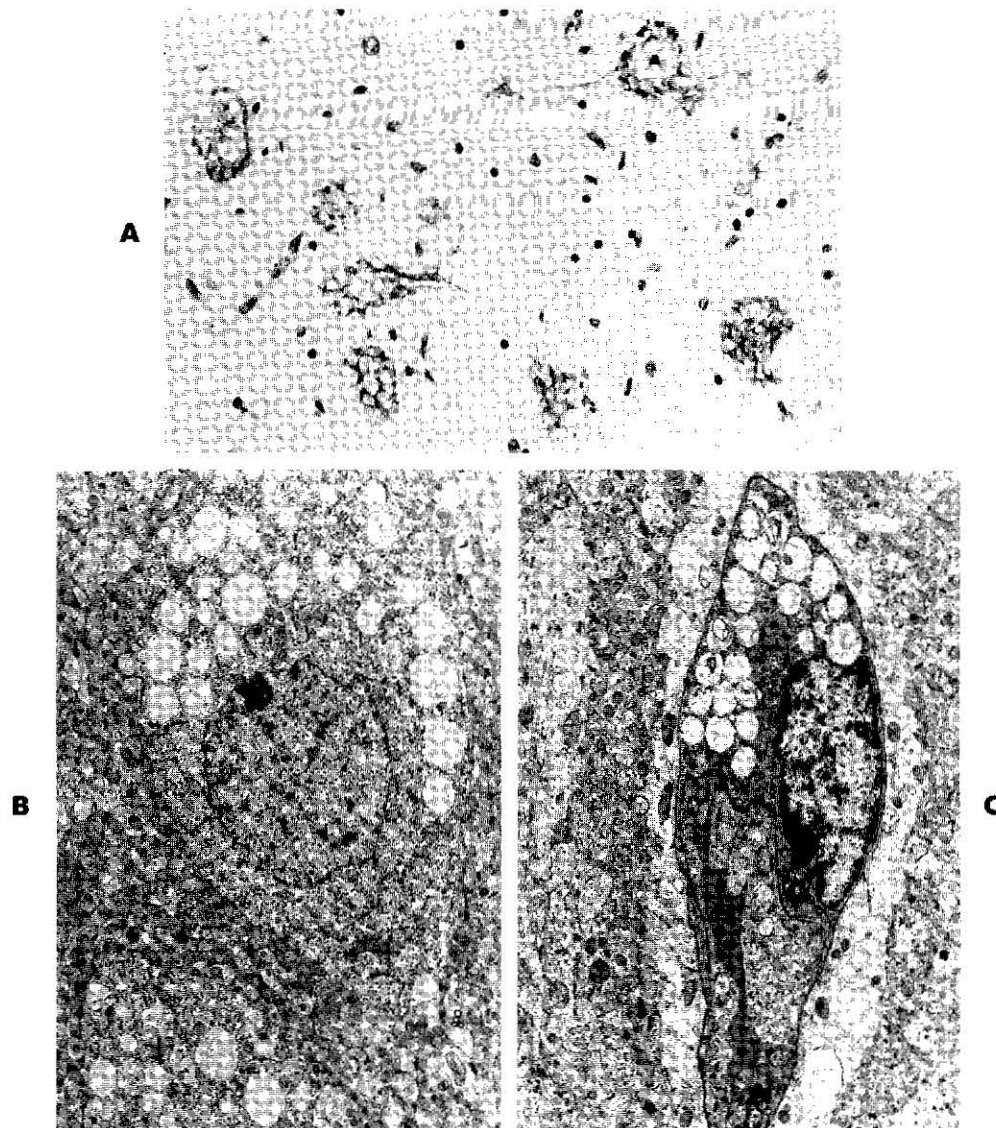


Fig. 5-14. Beta-mannosidosis, goat. **A**, Vacuolation of neurons in cerebellar nucleus. (Luxol fast blue, cresyl echt violet, $\times 350$.) **B** and **C**, Electron microscopic detail: **B**, Neuronal cytosomes, cerebral cortex. ($\times 3750$.) **C**, Vacuoles in vascular pericyte, cerebral cortex. ($\times 5625$.)

Ultrastructurally, the storage cytosomes (Fig. 5-14, *B*, *C*) vary from empty vacuoles to those with a few lamellar, granular, or more amorphous contents.^{153,154} Spheroids harbor a mixture of membranous whorls, electron-dense bodies, mitochondria, and filaments.¹⁵⁷ Ultrastructurally, hypomyelinated or nonmyelinated axons appear to be normal.¹⁵⁷ The effects of storage on the fine structure of the ear and the eye have been reported.^{158,159}

Failure of normal CNS myelination is not classically associated with lysosomal disorders except for globoid cell leukodystrophy. However, hypomyelinogenesis is a feature prominent in caprine β -mannosidosis and, to some degree, in mannosidosis in other animals. In affected goat kids, the central myelin defect has been demonstrated at 115 days of fetal life.¹⁶⁰ Postnatally, regions of the neuraxis most se-

verely affected are areas of white matter which are the last to myelinate. Accordingly, this hypomyelinogenesis seems to reflect the effects of a progressively worsening derangement that begins during fetal life. Degenerating oligodendroglia are not conspicuous in affected white matter, and so failure of their differentiation from progenitors is a more attractive hypothesis than is degeneration of a normally formed, full complement of these cells. The case has been made that fetal hypothyroidism in affected kids, revealed morphologically as progressive vacuolation of thyroid secretory epithelium, underlies this developmental hypomyelinogenesis.¹⁶¹ A similar hypothesis has been proposed in ovine hypomyelinogenesis (Border disease).

Affected goat kids have a recessive autosomal disorder of glycoprotein catabolism with very low levels of β -man-

nosidase activity in the CNS, liver, kidney, and plasma^{162,163} and with storage of oligosaccharides.

A storage disease affecting **Salers calves** from birth has been recognized in Canada, The United States, and New Zealand; affected calves have **β -mannosidosis**.¹⁶⁴⁻¹⁶⁶ Clinically, pathologically, and biochemically, they closely resemble the disorder in Nubian goats. Newborn calves cannot stand, have a pronounced head-bobbing activity, and may show whole-body tremors. In lateral recumbency, they may become opisthotonic. The calvaria is domed, and palpebral fissures are narrow. Postmortem findings are of variably severe hydrocephalus (lateral ventricle) and myelin pallor. The kidneys are markedly enlarged and have a greenish discoloration. Microscopically, the brain reveals a widespread cytoplasmic vacuolation of neurons, choroid plexus and ependymal cells, glial cells, axonal spheroids, and myelin deficiency.^{164,167} Beyond the nervous system, oligosaccharide storage vacuoles are pronounced in the thyroid, kidney, and dispersed macrophage populations. Lysosomal β -mannosidase activity is severely deficient in tissues and plasma.

Galactosialidosis

A single case of a novel, adult-onset lysosomal storage disorder has been reported in a 6-year-old female **Schipperke dog**.¹⁶⁸ The animal had presented 1 year earlier with a stumbling, ataxic gait. Some mononuclear cells in the CSF were vacuolated and contained metachromatic granules. At necropsy, LFB- and PAS-positive storage material was found in neuronal populations in the brain, spinal cord, and autonomic ganglia. Purkinje cells and granule neurons in the cerebellar cortex were depleted. Ultrastructural examination of cerebellar neurons revealed lamellated bodies within lysosomes. Brain homogenates from the affected dog contained depleted activity of **acid β -galactosidase**. The disorder may be comparable to human galactosialidosis, which is associated with the deficiency of a lysosomal protective protein.

Mucopolysaccharidoses

Proteoglycans are components of the connective tissue ground substance secreted by the resident population of cells. They consist of protein cores to which are attached molecules of acidic mucopolysaccharides (now known as glycosaminoglycans). Inherited disorders of lysosomal degradation of these compounds are known as the **mucopolysaccharidoses (MPS)**. Mucopolysaccharides are long chains composed of repeating disaccharide units, many of which are sulfated at C4 or C6, producing chondroitin, dermatan, heparan, and keratan sulfates.¹ Degradation of these large complex polymers requires the orchestrated activity of a number of lysosomal hydrolases; in humans, a number of MPS are recognized. As for most other storage disorders, these traits have an autosomal recessive pattern of inheritance with the exception of classical MPS II, which is X-linked.

In humans, **MPS I** results from deficiency of α -L-iduronidase and is manifest clinically as mild, intermediate, and severe forms; the last is known as **Hurler's disease**. **MPS II (Hunter's disease)**, which results from iduronate-2-sulfatase deficiency, occurs in mild and severe forms, and both are inherited as X-linked disorders. There is also an atypical form with autosomal inheritance. In both MPS I and II, dermatan and heparan sulfate accrue. Heparan sulfate accumulates in **MPS III or Sanfilippo disease**, which has at least four variants (A to D), all reflecting differing enzyme deficiencies: heparan-N-sulfatase (A), N-acetyl- α -D-glucosaminidase (B), acetyl CoA: α -glucosaminide N-acetyltransferase (C), and N-acetyl- α -D-glucosamine-6-sulfatase (D). **Morquio disease** is **MPS IV**, and it occurs in two forms; in Morquio A, N-acetyl-galactosamine-6-sulfatase and galactose-6-sulfate sulfatase activities are both diminished, whereas Morquio B results from a lack of β -galactosidase. In both types A and B, keratan sulfate is the major substrate to accumulate. A syndrome that was classified as MPS V has been reassigned to MPS I. Arylsulfatase B deficiency is the basis for **Maroteaux-Lamy disease** or **MPS VI**, which occurs in severe and intermediate forms and results in dermatan sulfate accretion; β -glucuronidase deficiency results in the storage of dermatan and heparan sulfate in **Sly syndrome** or **MPS VII**. Finally, a multiple sulfatase deficiency is recognized in humans, but the fundamental defect remains to be clarified.

Clinically, these patients present with diverse syndromes of varying severity. Skeletal abnormalities are the common denominator, resulting in abnormal facies with coarse features and shortened limbs; hepatosplenomegaly and mental retardation occur in some forms. Diagnosis of MPS requires the demonstration of abnormal storage in connective tissues and other organs, heightened excretion in urine, characteristic inclusions in circulating leukocytes¹⁶⁹ and other tissues, acquired by biopsy or postmortem, a demonstration of selective lysosomal hydrolase deficiency, and, in some cases, an abnormally high incorporation of sulfates into mucopolysaccharides in cultured cells.

In animals MPS is recognized in dogs, cats, goats, and laboratory animals. The common clinical theme consists of skeletal abnormalities including facial dysmorphism and locomotor difficulties. In **MPS I in domestic shorthaired cats**, the chief complaint is usually a pelvic limb gait disorder suggestive of skeletal disease. Examination at about 1 to 2 years of age also reveals bilateral corneal opacity and characteristic facial anomalies: a broadened and shortened maxilla, small ears, and, on profile, a depressed nasal bridge and frontal bossing.¹⁷⁰ The cat may resent palpation and manipulation of the skeleton, which has several radiographic abnormalities. Overt neurological deficits are usually lacking. Affected children are mentally retarded, but comparable evaluations have been difficult to make in affected cats. At necropsy, the liver and spleen are firm and enlarged, the meninges opaque, and the lateral ventricles of the brain may be dilated. A high frequency of meningiomas in cats with

MPS I (under 3 years of age) has been a curious observation.¹⁷¹ Lysosomal storage, presenting as cytoplasmic vacuolation, affects diffuse neuronal populations of the CNS, vascular pericytes, fibroblasts, hepatocytes, chondrocytes, keratinocytes, and bone marrow leukocytes.¹⁷² Ultrastructurally, the neuronal inclusions are membrane-bound stacked lamellae, so-called zebra bodies, which may be gangliosides, as in other tissues the soluble glycosaminoglycans leave largely empty cytosomes. The α -L-iduronidase activity is about 5% of that of control cats.¹⁷³

The absence of neurological signs such as behavioral disorders, cerebellar deficits, and seizures that are seen in other lysosomal storage diseases that compromise neurons (and other cells of the neuraxis) to a similar degree is striking. In cats with **MPS I**, cortical pyramidal neurons display meganeurites with ectopic neuritic processes,¹⁷⁴ changes thought to underlie some of the neurological derangements seen in lysosomal storage diseases. This all serves to emphasize how superficial our understanding is of how the clinical signs in these diseases are mediated. Shull and his colleagues have studied **MPS I** in **Plott hounds**. Somewhat akin to the feline disease, affected dogs had progressive corneal clouding, diminished mobility or significant lameness, and pain upon handling that were evident from 6 to 12 months of age. Carpal and tarsal joints were hyperextensible and the stance plantigrade. Neurological abnormalities were lacking despite widespread storage in meningo-epithelial cells, neurons, and astrocytes.¹⁷⁵ Polyarthropathy and skeletal abnormalities dominate the pathological picture, and synoviocytes contain incriminating cytoplasmic inclusions. Cardiomegaly and valvular degeneration are also found. There is severe α -L-iduronidase deficiency with elevated levels of mucopolysaccharides (dermatan and heparan sulfate) and some gangliosides in the CNS.¹⁷⁶ The cytosomes contain amorphous granular material or form zebra bodies with stacked membranes. The mode of inheritance in affected dogs is autosomal recessive,¹⁷⁷ and the syndrome is comparable to the intermediately severe form of Hurler's syndrome in humans.¹⁷⁸ Shull and associates have performed bone marrow transplantation studies in Plott hounds, using nonaffected littermates as donors.¹⁷⁹ The results have been encouraging, with clinical improvement and considerable diminution of degenerative joint disease, reduced vacuolar change in many visceral and nervous tissues, and close to normal levels and patterns of tissue mucopolysaccharides.¹⁸⁰

A single male Nubian goat with **MPS III** (Sanfilippo disease, D variant) has been studied at Michigan State University.¹⁸¹ The product of a father \times daughter mating, his neonatal disorder was marked by an inability to stand, a fine head tremor, mild horizontal nystagmus, and hypermobility of the shoulders. He learned to stand and walk, but his gait was ataxic, he was dwarfed, and he died at 19 months. Postmortem studies showed marked skeletal abnormalities. Storage cytosomes with lucent or membranous contents were found in neurons, myoid cells, fibroblasts, chondrocytes, and other cells. There was lysosomal storage

of sulfated glycosaminoglycans, and a deficiency of N-acetylglucosamine-6-sulfatase was demonstrated. There was also ganglioside storage (GM₃), believed to be a secondary defect.

MPS VI (Maroteaux-Lamy syndrome) has been studied in **Siamese cats**. The clinical signs largely reflect the widespread skeletal or other connective tissue disease, manifest as small body size, facial dysmorphism, kyphosis, corneal opacity, and a history of progressive difficulties in locomotion.^{182,183} Several affected cats have developed paraparesis between 4 and 7 months of age, with upper motor neuron signs in the pelvic limbs.¹⁸⁴ Myelography reveals narrowing of the subarachnoid space at the thoracolumbar junction. At necropsy, bilateral grayish areas of compressed, indented dorsolateral and ventral spinal cord funiculi corresponded to focal bony protrusions of the vertebral bodies into the vertebral canal.¹⁸⁴ Microscopically, the compressed thoracolumbar spinal cord showed neuronal depletion and Wallerian degeneration with astrocytosis in the white matter. Lysosomal storage affects circulating leukocytes and bone marrow cells, fibroblasts, and smooth muscle throughout the body with myelin-like, granular, or electron-lucent storage cytosomes¹⁸⁵ but spares the neuroectodermal population of the CNS. Wright-Giemsa-stained blood smears from affected cats reveal cytoplasmic vacuoles with metachromatic granules within granulocytes, lymphocytes, and monocytes.¹⁴¹ There is deficiency of fibroblast and leukocyte arylsulfatase B activity, resulting in dermatan sulfate accretion in tissues and elimination in urine.¹⁸³

MPS VII with β -glucuronidase deficiency was first recorded in a mixed-breed **dog**,¹⁸⁶ the product of a father-daughter mating. The clinical course was one of progressive weakness, skeletal abnormalities, and lack of overt neurological disturbance. There were elevated levels of chondroitin sulfates in the urine, a very low level of β -glucuronidase, and widespread lysosomal storage, including the CNS. Subsequently, further cases have been studied.¹⁸⁷ A **murine model of MPS VII** has also been described,¹⁸⁸ with stunted growth, facial dysmorphism, and shortened life span. The dramatic therapeutic benefits of gene replacement have been studied in **MPS VII**. A transgenic approach was used in murine **MPS VII** by introducing the human gene for β -glucuronidase.¹⁸⁹ In a different strategy, the effects of introducing retroviral vectors containing a rat β -glucuronidase cDNA was studied on cultured human and canine β -glucuronidase-deficient cells.¹⁹⁰ In both approaches, β -glucuronidase activity was expressed at therapeutic levels and corrected the phenotypic deficits.

Miscellaneous

Glycogenoses

A number of inherited human disorders are associated with abnormal storage of glycogen in a variety of tissues. Best known may be **Pompe's disease**, which is generalized glycogenosis type II, a consequence of deficient lysosomal α -1,4-glucosidase (acid maltase) activity.¹ Three patterns

are recognized: The infantile form (type IIa) has conspicuous cardiac involvement and is lethal by 1 or 2 years of age; in the juvenile (type IIb) and adult-onset (IIc) forms, cardiac failure is not a feature. There are at least eight types of glycogen storage disease with differing enzymatic disorders; only type II is lysosomal, and in all some storage of glycogen granules occurs free in the cytoplasm. In the glycogenoses, storage in the CNS and visceral tissues can be found, but involvement of voluntary, cardiac, and smooth muscle is prominent, and myasthenia is an important clinical feature of these disorders.

Generalized glycogenosis type II has been studied in **Shorthorn beef cattle** in Australia.¹⁹¹ Affected calves can be recognized before 12 months of age by virtue of progressive muscular weakness. They remain recumbent for abnormally long periods and, if forced to move, rise awkwardly and have a stumbling, staggering gait. Storage occurs in the CNS, but clinically it appears that weakness predominates over ataxia. Serum levels of muscle-specific enzymes are elevated, and in skeletal muscle biopsies, characteristic vacuolar changes are found in muscle fibers and peripheral nerves.¹⁹² It has been proposed that some calves qualify as the infantile pattern of Pompe's disease, as they succumb at a few months of age from heart failure with cardiomegaly, whereas other affected cattle have a later developing, more slowly evolving course of skeletal muscle weakness and can be compared to the juvenile form.¹⁹³

The diagnosis can be established by analyzing blood lymphocytes for 1,4-glucosidase activity and urine for glucose and by examining skeletal muscle biopsies. At necropsy, the carcass is wasted, and skeletal muscles may be pale, whereas cardiac dilation and hypertrophy are found in young calves that succumb with acute respiratory distress. Microscopically, there is widespread but variably severe cytoplasmic storage in the neuraxis, particularly involving large neurons in the brain stem and ventral horns of the spinal cord. Somata are markedly swollen and have a granular to vacuolar change that replaces normal Nissl aggregates. The storage cytosomes are strongly stained with Best's carmine or PAS and are diastase-sensitive; stains for lipid inclusions in frozen sections are negative. Vacuolar change also affects the cytoplasm of glial cells, including ependyma and choroid plexus epithelium and the tunica media of arterial blood vessels. In the cerebellum, storage in Golgi neurons is more conspicuous than in Purkinje cells, but some Purkinje cells are lost and reactive astrogliosis is evident. Scattered axonal spheroids are encountered from the diencephalon to the spinal cord. Storage is also to be found in the craniospinal ganglia, retinal ganglion cells, enteric and abdominal autonomic ganglia, liver, and kidney. Vacuolation distends the Purkinje fibers of the myocardium; myocardial and skeletal muscle fibers are swollen even to the point of disruption. Smooth muscle of the vascular bed and urogenital, alimentary, and respiratory tracts are also affected. Ultrastructurally there is evidence of particulate glycogen aggregation

free in the cytoplasm and in membrane-bound compartments (interpreted as secondary lysosomes) within cells of the CNS (neurons, astrocytes, oligodendrocytes) and PNS (Schwann cells, fibroblasts)¹⁹⁴ and in skeletal muscle. Fine structural changes in swollen axons are those common to many forms of axonal dystrophy, and the contribution from glycogen accumulation is minor. A deficiency in lysosomal enzyme activity is evident in the CNS, skeletal and cardiac muscle, and liver.^{191,194} This condition in Shorthorn cattle appears to be inherited as an autosomal recessive trait.¹⁹³

A condition pathologically and biochemically similar to this disorder has been recorded in **Brahman cattle** in Australia.¹⁹⁵ Abnormality was first noted at 2 to 3 months of age with poor body condition and lethargy. Affected calves subsequently became ataxic and hyperesthetic and developed muscle tremors, and these signs progressively worsened such that death by 9 months of age was common. It is of interest that neurological deficits seem to be more prominent despite histopathological changes comparable to those of Shorthorn cattle. Cardiomegaly was lacking, suggesting a juvenile (type IIb) phenotype.

Generalized glycogenosis type II was documented in **Lapland dogs** in the 1980s and had previously been recognized on morphological grounds.¹⁹⁶ Clinical signs are noted approximately between 6 and 18 months of age with an insidious onset. Muscular weakness was the hallmark, manifest as inactivity, disinclination to exercise, panting, rapid tiring, staggering, and collapse. Vomiting and passive regurgitation were common complaints, and radiographic studies showed megaesophagus.¹⁹⁷ Electrocardiograms demonstrated atrial fibrillation and premature ventricular beats; electromyography revealed prolonged insertional activity and bizarre, high-frequency discharges. Glycogen storage in tissues is comparable to that detailed for Shorthorn cattle, much apparently being lysosomal. Low leukocyte acid α -glucosidase activity can confirm the diagnosis and distinguish between most heterozygous carriers and normal homozygous Lapland dogs.¹⁹⁸

Glycogenosis type III has been identified in **German Shepherd dogs**. These pups had common histories of slow growth, poor body condition, weakness, and exercise intolerance from early life.^{199,200} Abdominal enlargement as a result of hepatomegaly was a common finding and the most remarkable gross abnormality at postmortem examination. Glycogen storage in smooth and striated musculature, CNS, and hepatocytes was found in nonlysosomal form. In one dog assayed, activity of the glycogen debranching enzyme **amylo-1,6-glucosidase** in liver and skeletal muscle was markedly depressed,²⁰¹ supporting this diagnosis (glycogenosis type III, Cori's disease).

A single case report describes widespread glycogenosis in a young, apparently healthy experimental cat.²⁰² Glycogen was demonstrated histochemically and ultrastructurally in CNS neurons and glia. **Glycogen storage disease type IV** was observed in **Norwegian forest cats**.²⁰³ Of three

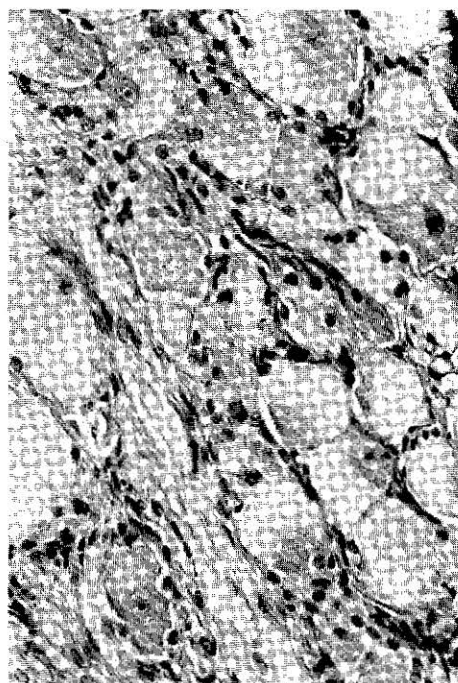


Fig. 5-15. Glycogenosis, cat. Fine vacuoles distend neuronal perikarya in a spinal ganglion. (H&E, $\times 350$.)

affected cats studied, two developed muscle tremors and weakness at 5 months of age and subsequently died with severe muscle atrophy and contractures. Branching enzyme α -1,4 glucan: α -1,4 glucan 6-glucosyl transferase was deficient, and storage in CNS, PNS (Fig. 5-15), and muscle was associated with marked degenerative changes.

Generalized glycogenosis was recorded in four **Corriedale sheep** examined at 6 to 10 months of age.²⁰⁴ Affected sheep were recognized by their poor constitution, lethargy, and mild ataxia. The disorder had been recognized in the flock for several years, and some had been found to expire acutely upon exertion. The findings at necropsy were of cardiac dilation and enlargement, and acute cardiac failure was invoked to explain the cases of sudden death. The microscopic and histochemical findings were as for glycogenosis type II (as previously described), which it was suggested this ovine storage disorder resembled; the study was retrospective, and fresh tissue for enzyme analysis was unavailable. Generalized glycogenosis has also been described in **Japanese quails**.²⁰⁵

Glycogen storage disease type VII has been studied in **English Springer Spaniel dogs**. Deficient dogs have erythrocyte defects, leading to hemolysis and intermittent hemoglobinuria.²⁰⁶ Evidence of pronounced myasthenia is lacking, although a single case has been described with a clinically evident myopathy.²⁰⁷

Ceroid-lipofuscinosis

Lipofuscin and ceroid are generically described as autofluorescent lipopigments, associated with the aging pro-

cess or resulting from the peroxidation of unsaturated lipids, respectively. Morphologically similar deposits, with analogous autofluorescent and histochemical properties, are found in a group of inherited storage disorders named ceroid-lipofuscinosis. Few areas in medicine are as confused, and it is not difficult to appreciate why misunderstanding abounds. Ceroid, age pigment, and neuronal ceroid-lipofuscin are heterogeneous substances, and they accumulate under distinct conditions. In spite of this, these terms have been interchanged, and assumptions that have been made with respect to the pathogenesis of these disorders have added to the confusion.²⁰⁸

It is well recognized that with advancing age, a yellow to brown granular pigment accumulates in the cytoplasm of neurons,²⁰⁹ cardiac muscle cells, and many other organs of the body. This "wear and tear" pigment is traditionally known as lipofuscin. Whether this age pigment is deleterious to the cells in which it accrues is uncertain.²⁰⁸ A morphologically similar pigment accumulates within the smooth muscle of the gastrointestinal tract in a variety of human digestive disorders. In this "brown bowel" syndrome, the pigment has been named either lipofuscin or ceroid,²¹⁰ and similar brown intestinal pigmentation occurred in dogs fed a high-fat diet.²¹¹ Traditionally, ceroid pigmentation is found within macrophages in association with lipogranulomas, with diets high in unsaturated fatty acids and low in antioxidants, and with steatitis.²¹²⁻²¹⁴

Because of the accumulation of lipopigments that resemble ceroid and lipofuscin in a group of inherited storage diseases, the term **neuronal ceroid-lipofuscinosis** was introduced. For many years, investigators have doubted that ceroid-lipofuscinosis is a true lysosomal storage disease, and, if this is indeed the case, it is yet to be established. In contrast to ceroid and age pigment accretion, clinical neurophthalmic diseases result from the excessive and widespread storage (and apparent toxicity) of ceroid-lipofuscin in neurons and glia of the neuraxis, retina, and other tissues. Many of these disorders present early in life (especially in humans), but a few are not evident until maturity or even advancing years, unlike most of the lysosomal storage diseases. Furthermore, the general principles upon which our understanding of this group of diseases rests have not been satisfied in this disorder; that is to say, that the substrate stored accumulates because of a derangement in a specific lysosomal hydrolase has not been shown. A popular explanation has been that these lipopigments represent end products of abnormal lipid peroxidation. The work of Jolly and his group has identified a lipid-binding protein, which is a component (subunit c) of mitochondrial ATP synthase, as constituting approximately 50% of the storage material in this disorder. Hence, the inherited ceroid-lipofuscinosis can be viewed as a proteinosis and, for the ovine variant (and a single bovine case) studied by Jolly's group in New Zealand, the designation proteolipid proteinosis can be applied.²¹⁵⁻²¹⁷ Hydrophobic amino acids in proteolipids impart lipid-like

properties, explaining many of the properties of this so-called lipopigment. Whether the disorder in other mammals conforms to this scheme will doubtless be clarified.

The classifications of human neuronal ceroid-lipofuscinosis are unusually prolific.²¹⁸ Subtypes have been designated descriptively, for example, **late infantile amaurotic idiocy**; eponymically, for example, **Batten** or **Kufs disease**; or by age of onset.⁹ The last includes **infantile**, **late infantile**, **juvenile**, and **adult** forms, and a comparable spread has been encountered in animals, most notably the dog. The human disease is marked by blindness, mental deterioration, seizures, and death. As the putative lysosomal deficiency is unknown, tissues and fluids cannot be screened antemortem to aid in establishing the diagnosis. However, characteristic inclusions have been demonstrated by ultrastructural examination of chorionic villi for prenatal diagnosis²¹⁹ and of patients' blood lymphocytes and urine sediment.^{220,221} Lymphocyte inclusions have also been recorded in canine ceroid-lipofuscinosis.²²²

In animals, ceroid-lipofuscinosis has been encountered most commonly in the **dog**, including English Setters,²²³⁻²²⁶ Border Collies,²²⁷ Salukis,²²⁸ Queensland Blue Heelers,²²⁹⁻²³⁰ Chihuahuas,²³¹ Yugoslavian Shepherds,²³² and Tibetan Terriers.^{233,234} In Dachshunds,^{235,236} unlike the preceding breeds, presentation at an older age has been noted. The clinical signs in Tibetan Terriers initially reflect nyctalopia (night blindness), and behavioral abnormalities evolve slowly over several years.²³³ Similar disease has been studied in **Siamese cats**,²³⁷ **South Hampshire sheep**,^{215,238} **Rambouillet sheep**,^{238a} **Devon cattle**,²³⁹ **Nubian goats**,²⁴⁰ and **primates**²⁴¹ (Fig. 5-16).

There is a common theme in the clinical presentation of this disorder, which has been studied most carefully in the **dog**, particularly Koppang's work with a large colony of English Setters. Presentation is often between 1 and 2 years of age. Blindness, or at least evidence of some loss of vision (perhaps nyctalopia), is one important hallmark. The other is abnormal behavior,²⁴² which encompasses depression or dullness, restlessness, nervousness, irritability and biting, inappropriate responses to background noises, and loss of learned behavior. Sometimes these dogs are described as demented and may be impossible to examine.²²⁷ Ataxia, head tremor, and hypermetric gait are often noted, attesting to a cerebellar component. The neurological deficits are progressive and accompanied by general loss of condition. English Setters, which first show signs at about 12 to 15 months of age, are often dead within a year. At craniotomy or necropsy, the cerebrum and/or cerebellum may be appreciably atrophied in chronic cases. Postmortem examination of the sectioned brain reveals a moderate expansion of the lateral ventricles and a yellowish discoloration of the parenchyma. There may also be lymphadenopathy²²⁴ with storage cytosomes in lymphoid organs and peripheral blood lymphocytes. Microscopic changes are somewhat variable between various canine breeds afflicted (population of neu-

rons affected, severity) and in the other affected animal species. Ceroid-lipofuscin deposition in neurons is common and in H&E-stained sections is seen as a grayish to pale yellowish brown granular cytoplasmic material. Sometimes it is weakly eosinophilic. The deposit is often polar and may extend into the axon hillock or the base of primary dendrites. In some cases, displacement of the nucleus and Nissl bodies to the cell margin and pyknosis of the nucleus are seen.²³⁵ However, it is common to find neurons that have accommodated the granular deposits without apparent degeneration or displacement of organelles. These cytoplasmic deposits give a yellow autofluorescence with ultraviolet light, stain positively with PAS and Sudan black stains, and are weakly acid-fast, usually both in frozen and paraffin sections. The deposits are very clearly demonstrated with Luxol fast blue, the dark blue staining perhaps attesting to the proteolipid component of the substrate.²¹⁵ Surprisingly, in a Tibetan Terrier that showed only visual deficits, extensive storage was demonstrated in multiple neuronal populations.²³³ Ischemic-type change in scattered cerebrocortical neurons was another unexpected observation, although Taylor and Farrow²²⁷ commented upon some degree of loss of these cells in affected Border Collie dogs.

Perhaps more striking in ceroid-lipofuscinosis than most lysosomal storage diseases is the degree of neuronal necrosis; storage appears to be cytotoxic to some populations, or other mechanisms of cell killing are activated. Depletion is generally most evident in cerebellar cortical Purkinje cells; clusters of astrocytes and scavenger macrophages aggregate where these neurons have disappeared. In two affected Dachshunds, however, there was relative sparing of Purkinje cells,²³⁶ attesting to the variation within this syndrome. Granule cell necrosis may also be seen but usually is less severe. Scattered axonal spheroids are found in cerebral and cerebellar white matter.

Ultrastructurally, the neuronal membrane-bound cytosomes are a triad of membranous, granular, and lipoidal components, sometimes appearing as typical lipofuscin but accumulating excessively for the animal's age. The membranous elements are comprised of stacks of trilaminar or pentilaminar membranes, which form the characteristic fingerprint or curvilinear profiles. The granular component is amorphous and commonly contains globules of lipid-like material. Occasionally zebra bodies are also found. Storage granules are found in lower numbers in astrocytes and endothelial cells. In contrast, the contents of macrophages are more vacuolar, with lesser quantities of lipofuscin. The intervening neuropil shows a status spongiosis, in part resulting from swollen processes of reactive astrocytes.

Storage is also found in the retina (mainly ganglion cells),^{234,243} autonomic ganglia, sometimes parenchymal cells of organs such as the kidney, liver, and pancreas, and smooth muscle fibers.²²⁶ Diagnosis requires biopsy or necropsy examination, as the underlying enzymatic disorder is yet to be determined. Where multiple cases in animals

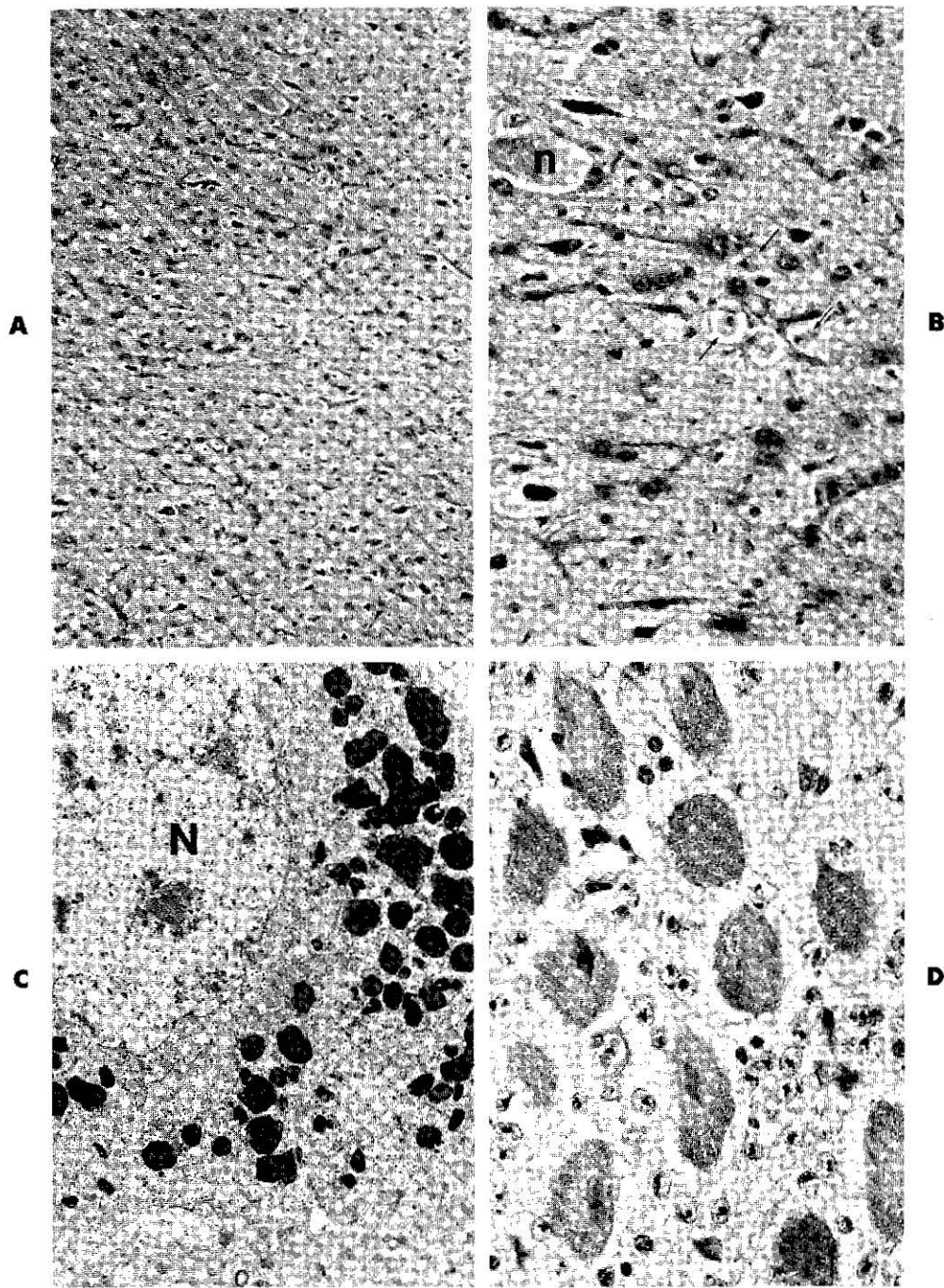


Fig. 5-16. Ceroid-lipofuscinosis. **A**, Cerebral cortex, cat. Extensive neuronal loss with reactive astrogliosis. (H&E, $\times 140$.) **B**, Detail showing a single surviving neuron (*n*). A few macrophages are evident (*arrows*). (H&E, $\times 350$.) **C**, Ultrastructural detail of ceroid-lipofuscinosis, dog. Note nucleus of neuron (*N*). ($\times 5625$.) **D**, Cow. Granular storage in cerebellar Purkinje cells. (Luxol fast blue-PAS, $\times 560$.)

have been studied, an autosomal recessive mode of inheritance has been proposed. Both sexes are affected.

Clinically and pathologically similar cases have been described in two **Siamese cats**,²³⁷ but reports of ceroid-lipofuscinosis in the cat are rare. Harper and others²³⁹ have described the disease in **Devon cattle**, which from 14 months of age were found to be blind, walk in circles, and have a head tilt. Ophthalmoscopic examinations showed severe retinal degeneration that was confirmed postmortem. The retina was severely atrophic with depletion in all nerve cell layers. Storage granules were found in surviving ganglion cells, throughout the CNS, and in nodal histiocytes, liver, and kidney. As in some dogs with ceroid-lipofuscinosis and South Hampshire sheep, a mild loss of neurons from cerebrocortical laminae was noted. As well as storage in somatic motor neurons of the spinal cord, there was mild Wallerian degeneration in the lateral and ventral funiculi. A neuronal lipodystrophy in a blind **Beefmaster bull**²⁴⁴ may also have been a case of bovine ceroid-lipofuscinosis.

Jolly and his group have exploited the **ovine** variant as a model of Batten's disease,^{215,216,238} for both the ophthalmic and neuraxial components. By careful examination, visual deficits can be detected in affected lambs at 7 months of age that progress to obvious blindness with dilated pupils, depression, circling, and head tremors. Brain atrophy can be demonstrated at 4 months and is progressive to termination at around 25 to 30 months of age. The brain may weigh but half that of an age-matched control, the loss being mainly prosencephalic. It is yellow-brown, attesting to the widespread storage and firm, reflecting reactive fibrillary gliosis. GFAP preparations clearly highlight areas of cortical neuronal loss. There is retinal degeneration with atrophy of outer segments and loss of photoreceptor cells, and so visual loss probably has both central and retinal components. Light and fine structural features are as discussed for the canine patterns.

Neuronal ceroid-lipofuscinosis has been reported in two related, mature **Nubian goats**²⁴⁰ with behavioral abnormalities, ataxia, and paresis. Storage was maximal in neurons of the brain stem and the ventral gray column of the spinal cord. In a single **cynomolgus monkey** clinically normal at the time of euthanasia (a control animal in a pharmaceutical study), widespread neurovisceral ceroid-lipofuscinosis was demonstrated by microscopy and histochemistry.²⁴¹

In contrast to the above, acquired ceroid-lipofuscinoses have been described in animals that are believed to be due to dietary or other environmentally acquired neurotoxins. An ataxic disorder of **horses** has been recognized in the **Gomen** township of New Caledonia for more than 40 years.²⁴⁵ Affected horses graze valley areas in the north-western part of the island. Animals confined in village areas are spared. Clinical signs range from mild to severe, slowly

progressive pelvic limb ataxia. In severe cases, the forelimbs may also be affected. A clinical course of 3 or 4 years or even longer is common, progressing finally to death by misadventure or starvation. At necropsy, the cerebellum may be small, with atrophy of the vermis. Microscopic findings are of depletion of Purkinje and granule cell neurons of the cerebellar cortex.²⁴⁶ Remaining Purkinje cells often contain dense cytoplasmic deposits of a granular red to brown pigment. Some Purkinje cells are replaced by large cytoplasmic vacuoles. The stored material, found also in macrophages and in other neurons, hepatocytes, and renal tubular epithelium, is PAS-positive and acid-fast. Significant findings are not observed beyond the cerebellum, apart from a Wallerian degeneration in the spinal cord. Ultrastructural evaluation of the cytosolic pigment reveals lipoidal and membranous deposits with the hallmarks of lipofuscin. Cells in the cerebellar molecular layer also contain concentric membranous lamellae resembling membranous cytoplasmic bodies, a hallmark of the gangliosidoses, but also acquired in *Solanum* poisoning of cattle (see elsewhere in this chapter).

Epidemiological observations suggest that this is an acquired cerebellar atrophy of horses, developing perhaps 1 or 2 years after grazing in this geographical area of New Caledonia. Cattle raised in this district are apparently unaffected. The syndrome is thought to be an exogenous lipofuscinosis of Purkinje cells, storage progressing to the ultimate demise of these cells. A plant poisoning is suspected, perhaps involving also a heavy metal; this island is rich in heavy metals, which could be concentrated in certain plants. The clinical signs appear to reflect diffuse spinal cord white matter disease with proprioceptive loss rather than pure cerebellar ataxia.

A condition presenting as progressive paresis in **sheep** and **horses** has been described from western Australia.²⁴⁷ There is severe weakness, which results in a crouched posture, muscle fasciculations, and a staggering gait. Affected animals have a profound neuronal lipofuscinosis that is widespread in the CNS and also affects spinal ganglia and enteric neurons. It is interesting to ponder how such might produce what clinically resembles neuromuscular disease; perhaps the clinical effects result from a separate effect from that causing the pigment storage. This disorder occurs in animals that consume branched onion weed (*Trachyantra divaricata*). In South Africa, similar syndromes have been associated with the plants *T. laxa* and *T. divaricata*.^{248,249} horses, pigs, and goats have also been poisoned. Italian workers²⁵⁰ observed a neurological disorder of sheep during a particularly dry season. Animals showed ataxia and seizures, and pathological studies showed neurovisceral lipofuscinosis, which was thought to be acquired.

References are on page 329.

CENTRAL NERVOUS SYSTEM HYPOXIA, ISCHEMIA, AND RELATED DISORDERS

Introduction

Neonatal maladjustment syndrome in foals
Anesthesia-related syndromes
Feline ischemic encephalopathy
Cerebrovascular accidents
Seizures and cerebral necrosis
Hypoglycemia
Encephalomalacia following intracarotid injection in horses
Fibrocartilaginous embolic myelopathy
Traumatic feline ischemic myelopathy

Introduction

When tissues are rendered **hypoxic**, their oxygen supply is diminished below that required for normal physiological activity. In most forms of hypoxia, such as that caused by carbon monoxide poisoning or resulting from cardiac arrest, the effects on the brain are global, although not all regions are equally susceptible to the insult, and the spinal cord is less sensitive than is the brain.¹ Neonatal animals are more resistant to hypoxia than are adults; this may be a consequence of their lower cerebral metabolic activity,² their ability to utilize lactate (which accumulates in hypoxia) as a substrate for energy, or their high content of ascorbate, which may be protective.³ **Cerebral ischemia** is the reduction (not necessarily cessation) of blood flow to a level incompatible with normal function. Again, the impairment to the brain may be global or regional.⁴ Several factors bear on cerebral blood flow: systemic blood pressure, vascular patency, intracranial pressure, and the capacity for autoregulation.⁵ With falling blood pressure, cerebral arterioles dilate to maintain perfusion but below 50 mm Hg can accommodate no further and cerebral blood flow declines linearly with systemic arterial pressure.⁶ Simplistically, ischemia can be viewed as hypoxia plus hypoglycemia and is particularly devastating to the brain, which has the highest energy demands of all organs. Hypoxia and ischemia (often considered together as **hypoxia-ischemia**) first impair the most sensitive elements in the tissue and, if severe, persistent, or both, perturb all components. The neuroectodermal cells most sensitive to such metabolic derangements are neurons, particularly certain populations. Of the glial cells, oligodendrocytes are the most vulnerable, astrocytes are somewhat more resistant, and mesodermal microglia and fibrovascular elements are even more so. In myelinated fibers, the axon is more sensitive than its myelin sheath.

Severe ischemia, which in the CNS would produce necrosis of neurons and glial elements, results in an area of dead tissue described as an **infarct** (Figs. 5-17 and 5-18). Severe arterial hypotension produces bilateral infarction in the boundary or **watershed zones** between major arterial territories.⁶ If there is pre-existing vascular compromise, the

hypotension need not be so severe, there may be asymmetry in the distribution of the infarcts, and they may fall partly or entirely within arterial territories. Elevation of the local concentration of lactic acid may be important in the transition from cerebral ischemia to cerebral infarction, although on this point there is not universal agreement; moderate acidosis may even be neuroprotective.⁷ Repeated episodes of ischemia seem to produce cumulative injuries that can progress to infarction.

Common sense would dictate that the restoration of blood supply to an area of infarction would best facilitate recovery. Were life so simple! There is evidence that interactions between blood constituents and the damaged tissue can lead to further insult—so-called **reperfusion injury**—and this can occur in the brain, heart, and other organs. Several potential factors have been suggested that could mediate these effects, including leukocyte products, free radicals, and Ca^{++} .⁸⁻¹⁰

Since the early 1970s, progressively accumulating knowledge has been pointing to the **excitatory neurotransmitters** as important final mediators of neuronal death in hypoxia, ischemia, hypoglycemia, seizures, and some other human neurological disorders.^{11,12} Evidence for the role for excitotoxicity is particularly strong for those conditions leading to acute neuronal death.¹³ The main perpetrator of excitotoxicity is believed to be **L-glutamate**, although **L-aspartate** may also be involved, especially in hypoglycemic disorders. Numerous studies in dissociated brain cultures, brain slice preparations, and in vivo have demonstrated that excitotoxic neurotransmitters or analogues of these amino acids have the potential to produce neuronal necrosis. Glutamate acts via one of three membrane receptors that are named for their most potent agonists: kainate, N-methyl-D-aspartate (NMDA), and quisqualate. The excitatory effects of glutamate can be blocked with specific antagonists for these receptors. Importantly, these antagonists also protect neurons against the lethal effects of ischemia, hypoxia, and so on. Axotomy, which destroys the afferent source of these excitatory neurotransmitters, will equally safeguard against this form of injury. This excitotoxic hypothesis attractively accounts for the common topographic territory in the brain that is prone to injury in this group of diseases, neuronal susceptibility being determined by a membrane receptor for glutamate, particularly on dendrites. In cerebral ischemia, neurons in the center of the lesion probably succumb to the direct effects of failed perfusion, whereas those in the marginal zone are killed by excess glutamate. Tissue culture studies indicate that oligodendrocytes are also vulnerable to glutamate-induced necrosis.

It is believed that there are two patterns of excitotoxin-mediated neuronal injury:

1. Acute damage, which is associated with the entry of Ca^{++} and Na^{+} (which are followed by Cl^{-} and water), resulting in osmotic cell swelling and lysis
2. A more slowly evolving cell injury mediated by the



Fig. 5-17. Cerebellar infarct, dog. ($\times 4$)

evated levels of intracellular calcium with activation of Ca^{++} -dependent proteases,¹⁴ phospholipase, and free radicals

The conditions under which neurotransmitters become neurotoxins have been investigated. With hypoxia-ischemia, hypoglycemia, energy depletion, and the like, glutamate release is increased while uptake declines. Neurotransmitters released into the synaptic cleft are normally recycled by uptake into nerve processes and glia. In tissue culture, neurons become much more sensitive to excitotoxic effects of glutamate if astrocyte numbers are depleted,¹⁵ possibly pointing to their important role in degrading glutamate to glutamine. Furthermore, glutamate becomes neurotoxic when neuronal energy content is depleted and Mg^{++} -dependent blockade of the NMDA receptor channel is lost.¹⁶ There is also evidence incriminating nitric oxide as a mediator of direct neuronal degeneration, although not of ischemia, following NMDA receptor activation.^{17,18}

In ischemia, the failure of cellular energy sources (such as ATP) stimulates anerobic glycolysis, disrupts ion ho-

meostasis, and leads to the breakdown of cell structure.¹⁹ Hypotheses as to the mechanism of hypoxic-ischemic neuronal injury are lactic acidosis, calcium influx, oxygen-free radicals, and excitotoxins,²⁰ proposals that are not necessarily mutually exclusive.

In humans, it has been recognized for some years that there are regions of vulnerability within the brain where neurons are prone to be injured by global hypoxia-ischemia, hypoglycemia, and seizures. These areas are the cerebral cortex, especially neuronal laminae II, III, and V, populations in the hippocampus, the amygdala, some other basal nuclei, some thalamic nuclei, and the cerebellar cortical Purkinje cells. Specific zones of neuronal populations within these broad fields have been identified because of their particular vulnerability to certain forms of injury; for example, the pyramidal neurons of the hippocampus in CA1 sector are particularly vulnerable to ischemic injury, while the CA3 pyramidal cells and dentate granule cell neurons are relatively resistant.²¹ Such a selective vulnerability in the hippocampus of domestic animals has not been described, with

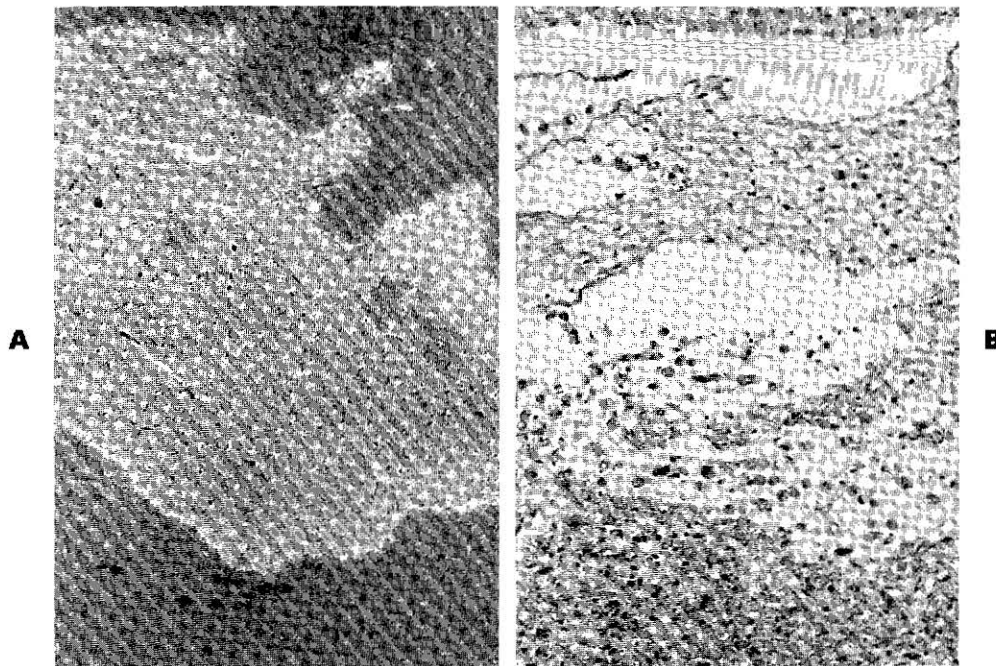


Fig. 5-18. **A**, Ischemic infarct in the internal capsule, sheep. Infarcted tissue is pallid and sharply demarcated from normal tissue. (H&E, $\times 35$.) **B**, Old cavitated cerebral infarct, dog. The cavities contain a few blood vessels and gitter cells. (H&E, $\times 140$.)

very rare exceptions.²² Studies of ischemia, hypoglycemia, and seizures in laboratory animal models also point to differences in the distribution, nature, and temporal evolution of brain injury with these three disorders.²³ Ischemic injury is much more potent than hypoglycemia or seizures in that only a few minutes of ischemia are required to produce neuronal necrosis. However, ischemic changes may not appear for 1 to 2 days after the event, whereas neuronal death can be found within an hour of a severe seizure.

Efforts to differentiate these varying forms of neural injury on pathological grounds (e.g., hypoglycemic vs. hypoxic brain injury)²⁴ have met with varying degrees of acceptance. The terminology is potentially confusing because the stereotyped response—swelling of perineuronal astrocyte foot processes, neuronal contracture, cytoplasmic eosinophilia, nuclear pyknosis, karyolysis, and cell dissolution—is referred to as **ischemic cell change**, regardless of whether or not the brain injury results from obstruction to vascular perfusion, that is, ischemia. The term **energy-deprivation change** may be somewhat more suitable and is appropriate for conditions in which oxygen, glucose, or other essential nutrients (e.g., thiamine) are not delivered to the neuron and intracellular energy levels (e.g., ATP) fall significantly. In seizures, however, neuronal injury probably results from abnormally heightened activity plus the secondary effects of the seizure activity (pyrexia, hypoxia, hypoperfusion).

Ischemic cell change occurs rapidly, particularly in small neurons. The earliest neuronal indication of ischemic change

is microvacuolation of the cytoplasm. This occurs in a matter of minutes after the insult. Usually the vacuoles are manifestations of mitochondrial swelling, although dilated profiles of endoplasmic reticulum also contribute to this cytoplasmic change. The cytoplasmic matrix increases in density, the cell body shrinks slightly, and clear, swollen astrocyte processes²⁵ highlight the perimeter of the darkening neuron in such a way as to suggest the presence of a perineuronal space. Neuronal shrinkage becomes more prominent with time, and perikaryal staining increases. In H&E-stained sections, the affected somata are pink or red. With cresyl violet, the shrunken cells are more deeply and uniformly stained, and they also are more deeply impregnated with silver. The nucleus is shrunken, densely heterochromatic, and often triangular. The nucleolus cannot be discerned with the light microscope. Apical dendrites may present a shriveled or condensed, twisted appearance in the cerebral cortex. Fink-Heimer or Nauta staining suggests that these condensed dendrites fragment.

The shrunken, microvacuolated cells undergo breakdown of granular endoplasmic reticulum (ER) and eventually may lose most discernible organelles in their increasingly dense cytoplasm. These dense perikarya become progressively irregular in outline as swollen astrocyte processes invaginate or invade their cytoplasm. As a result of the astrocytic incursions, dense, irregular cytoplasmic protrusions develop around the perimeter of the neuron (Fig. 5-19). In the past, these dense neuronal projections, which are highlighted by pale astrocyte processes, were mistaken for points where

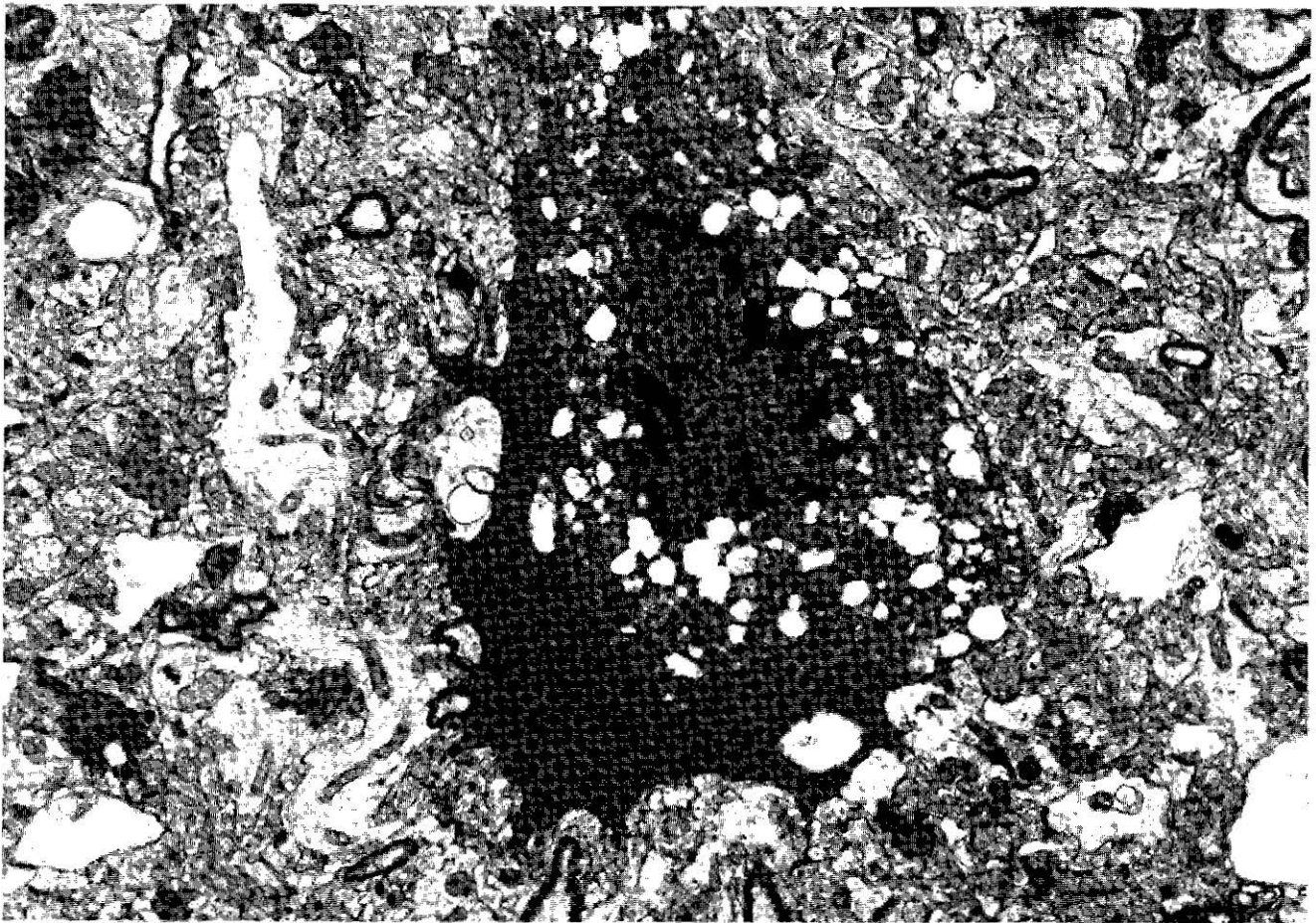


Fig. 5-19. Ischemic neuron, rat. The nucleus is pyknotic and dark; condensed cytoplasm is pocked by invaginations of astrocyte processes. Surrounding neuropil is intact. ($\times 8800$.)

synaptic connections were effected by terminal boutons.²⁶ These configurations were called incrustation of the Golgi network. The deep astrocytic invaginations appear to subdivide the neuron, and the appearance of proximate microglia and mononuclear cells suggests that neuronal fragmentation and phagocytosis are imminent.

Specific disorders of animals encompassed by the broad title of this section will now be discussed.

Neonatal maladjustment syndrome in foals

The neonatal maladjustment syndrome (NMS) is a well-recognized but poorly understood disorder of neonatal foals. Typically, affected animals are normal at birth but during the first day postpartum (and sometimes within minutes of delivery) develop a number of clinical abnormalities. Occasionally the foal is normal for the first few days of life.²⁷ These signs have resulted in a number of designations for these animals, including **barker and wander foals**, **dummy foals**, and the **convulsive foal syndrome**. Affected foals become disinterested in suckling and may wander aimlessly, apparently blind. Some elicit a peculiar barking sound and

have respiratory difficulties. Deterioration is marked by recumbency and seizures with opisthotonic posturing, which progress to coma and death, although recovery from a comatose state may occur.²⁸

The neuropathological findings vary with the length of the clinical illness. With an acute course of a day or so, the brain is marked by hemorrhages in the cerebrum, cerebellum, basal nuclei, and midbrain. Both gray and white matter are affected. However, neuraxial hemorrhages in foals probably have a number of causes, and birth trauma may be a major cause.²⁹ Accordingly, the observation of hemorrhage alone (especially of limited extent) is less diagnostically specific. In foals surviving for several days with seizures, there is cerebrocortical necrosis.²⁸ This begins with a laminar edema in the neocortex and progresses through ischemic neuronal change to massive liquefactive necrosis of middle and deep laminae. Scattered mineral-encrusted neurons will be encountered (Fig. 5-20, A). These lesions are widespread in the dorsal and lateral cortical ribbon, and, given the severity of neuronal loss, it is remarkable how well the corona radiata survive. Similar ischemic neuronal degen-

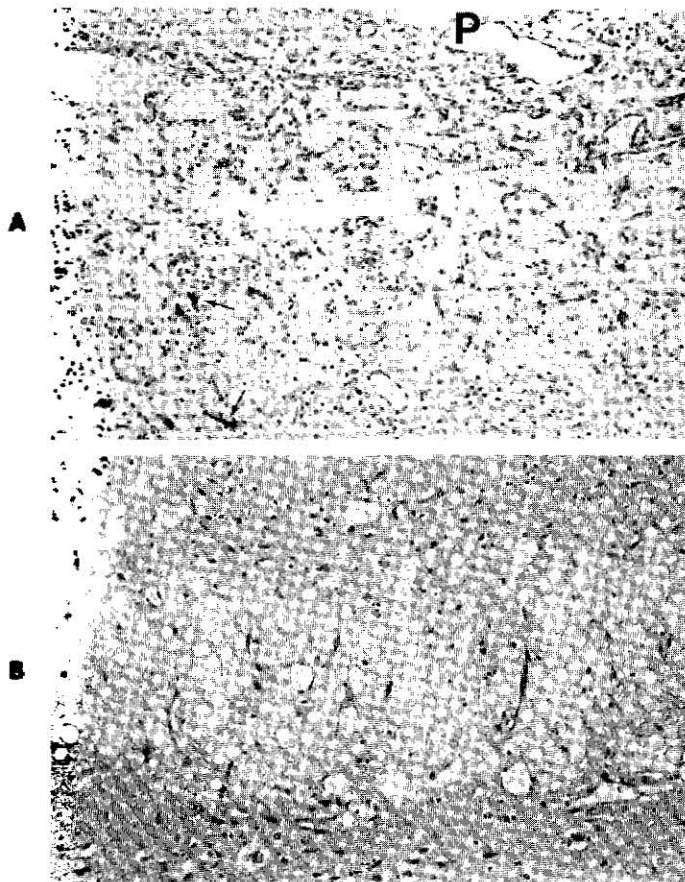


Fig. 5-20. Cerebral hypoxia. **A**, Neonatal maladjustment syndrome, foal. Necrosis and cavitation of the cerebral cortex (pia mater, *p*). Some neurons are encrusted (*arrows*). (H&E, $\times 140$.) **B**, Laminar vacuolar degeneration of cerebral cortex secondary to dystocia, calf. (H&E, $\times 140$.)

eration is found with less regularity in the hippocampal gyrus, caudate nucleus, thalamus, amygdala, medial and lateral geniculate nuclei, and the colliculi.

The pathogenesis of NMS is not known. There was interest at one time in the thought that it may represent a pulmonary surfactant disorder, but that idea has lost favor.³⁰ It seems hard to avoid the conclusion that the cerebral insult is hypoxic. Figure 5-20, *B* demonstrates the effects of cerebral hypoxia at birth (resulting from dystocia).

Anesthesia-related syndromes

A number of post-anesthetic neurological disorders have been recognized in animals. Fortunately, these are sporadic, but they are an embarrassment whenever they occur. Most common are the **anesthetic accidents** in which intubated animals receive inhalant gases largely or totally devoid of oxygen. It seems that a period of hypoxia of 5 minutes or more is lethal to neurons. Palmer and Walker³¹ have published their experience with five animals that suffered an episode of cardiac arrest while under anesthesia; in one of these cases, arrest was caused by a failure of the oxygen

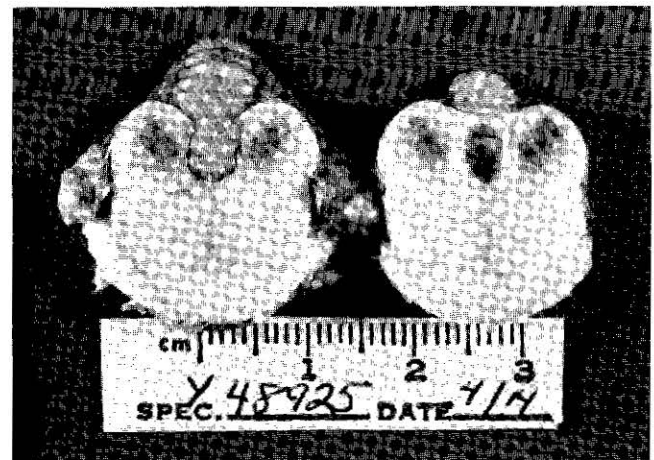


Fig. 5-21. Anesthetic accident, dog. Hemorrhages in caudal colliculi.

supply. Whether from anesthetic accident or cardiac arrest, the clinical outcome is similar. Upon recovery from anesthesia, such animals are blind and may initially have dilated pupils, which later constrict. Some are recumbent, with postures varying from stiffness to decerebrate rigidity, and seizures may occur. The dystonia may improve with time, but the visual loss is usually permanent. If such animals are euthanized, they are found to have an encephalopathy (Fig. 5-21) that can be mapped to those areas of the brain (described earlier) sensitive to energy deprivation of neurons. Microscopically, the stereotyped response is found: intense neuronal cytoplasmic eosinophilia, shrinkage, nuclear pyknosis, neuronal dissolution, liquefaction of the neuropil, prominent neovascularization, and a macrophage reaction. Middle and deep neuronal laminae are particularly sensitive. Similar changes afflict neuronal populations in the subcortical populations listed. White matter adjacent to areas of neuronal hypoxic necrosis is edematous, and GFAP preparations show a marked astrogliosis.

Cerebrocortical necrosis extends from the frontal to occipital lobes. The cingulate gyrus is typically spared, as are the lateral and ventral gyri, such as the pyriform lobe and parahippocampal gyrus. Watershed areas may be most prone to the effects of lowered oxygen tension; the endogenous excitatory neurotransmitters are probably involved in mediating neuronal necrosis.

Clinicians and pathologists in Switzerland, England, and the United States have observed a **post-anesthetic hemorrhagic myelopathy in the horse**.³²⁻³⁴ There is a common theme of young horses undergoing general anesthesia for routine surgical procedures. All horses that developed a myelopathy were placed in dorsal recumbency for the duration of the anesthesia. Immediately following recovery from the anesthetic and removal of the endotracheal tube, these horses were alert and had use of their thoracic limbs but were unable to stand because of pelvic limb paralysis.

The affected limbs were extended and either spastic or flaccid. In the latter case, patellar reflexes were lacking, and pelvic limbs showed no evidence of pain or withdrawal from a noxious stimulus. In one horse³⁴ the myelopathy extended from C6 to T8, and so the pelvic limbs were stiff with UMN paralysis. In other cases the lumbosacral gray matter was necrotic, producing LMN signs.

Affected horses were killed, and postmortem examination revealed an acute hemorrhagic poliomyelopathy that was most consistent, and most severe, in the thoracic segments. Grossly the affected spinal cord appeared hemorrhagic in the gray matter when transverse sections were examined. Hemorrhages were found also in the meninges. Microscopically, there was hemorrhage and acute neuronal degeneration in the central gray matter. The vertebral venous sinuses were distended, and the disorder appears to be one of pronounced venous stasis, producing a venous infarction of the spinal cord. The dorsal posture seems to be a critical factor, perhaps because it would impede drainage of the caudal vena cava and/or azygous vein because of the weight of abdominal viscera.

We have observed four instances of a novel syndrome of extensive **post-anesthetic cerebral necrosis in adult horses**. All four were placed under general anesthesia for variable periods of time. Three had abdominal surgery for colic and one for attachment of an orthopedic prosthesis. At no time were any anesthetic complications observed. All horses made full, normal recovery from the anesthesia and were returned to their stalls. From 2 to 7 days following this anesthetic and surgical experience, these horses suddenly developed severe signs of a predominantly cerebral disturbance: bilateral blindness with normal pupillary light responses, abnormal behavior varying from propulsive pacing and circling to head pressing and profound lethargy, and generalized seizures. All four were euthanized between 3 days and 3 weeks following the onset of these signs, which persisted unchanged.

At autopsy, gross examination of some brains revealed patchy areas of cerebral cortex and adjacent white matter that were soft and sometimes discolored (Fig. 5-22). On microscopic examination, all showed lesions that varied from laminar necrosis in the cerebral cortex to more diffuse necrosis of the cortex and underlying white matter.

The cause of this lesion is presumed to involve a compromise of the cerebral circulation, but the specific nature of the compromise and its relationship to the surgical and anesthetic experiences are unknown.

Other post-anesthetic complications in the horse are worthy of brief mention: prolonged periods of recumbency can produce **peripheral nerve compression** and neurapraxis, such as to the facial nerve, and so the sensitive area of the animal must be carefully padded. Further, a syndrome of **equine post-anesthetic myopathy** has been documented.^{35,36} Some cases may result from direct pressure-induced muscle necrosis, whereas ischemia is implicated in others.³⁷



Fig. 5-22. Post-anesthetic cerebral necrosis, horse. Multiple petechiae, necrosis and cavitation (arrows), cerebrum. Necrosis of caudal colliculus (arrow).

Feline ischemic encephalopathy

Feline ischemic encephalopathy is described in textbooks of veterinary medicine and neurology, but only occasional case reports have been published.³⁸ The disorder seems to spare kittens but affects adult cats of either sex. Affected animals are presented at all times of the year, but in our experience a distinct peak occurs in the summer months; the reason is not known but may hold a clue to the etiology. This is a syndrome of cerebral infarction, and the presenting signs vary with the degree and distribution of tissue destruction. Accordingly, clinical signs (which develop precipitously) vary from simply depression and a brief course of mild paresis and ataxia to pronounced behavioral change (often aggression), seizures, and blindness. Involvement of the rostral thalamus or frontal lobes can induce propulsive pacing and sometimes circling. At the onset, some cats are pyrexemic. As in humans with strokes, the disorder is often nonfatal, and many cases show some resolution of their cerebral disturbance. Consistent with a vascular disorder, the course is nonprogressive, but in some cats seizures or aggressiveness persists; such cases are often those that become available for neuropathological study.

Gross examination of the intact brain often shows appreciable asymmetry of the cerebral hemispheres, particularly in cats that have survived for weeks after the event. This asymmetry results from a regional destruction of the cerebrum, producing a sunken, depressed area, typically in the parietal-temporal field (Fig. 5-23). Examination of the serially transected brain better demonstrates the extent and distribution of the lesions. Cerebral necrosis may be found bilaterally, but, if so, there is usually marked asymmetry, and the deficits that can be detected on neurological examination (postural deficit, menace loss) are lateralizing to the cerebrum which bears the brunt of the infarction. Quite

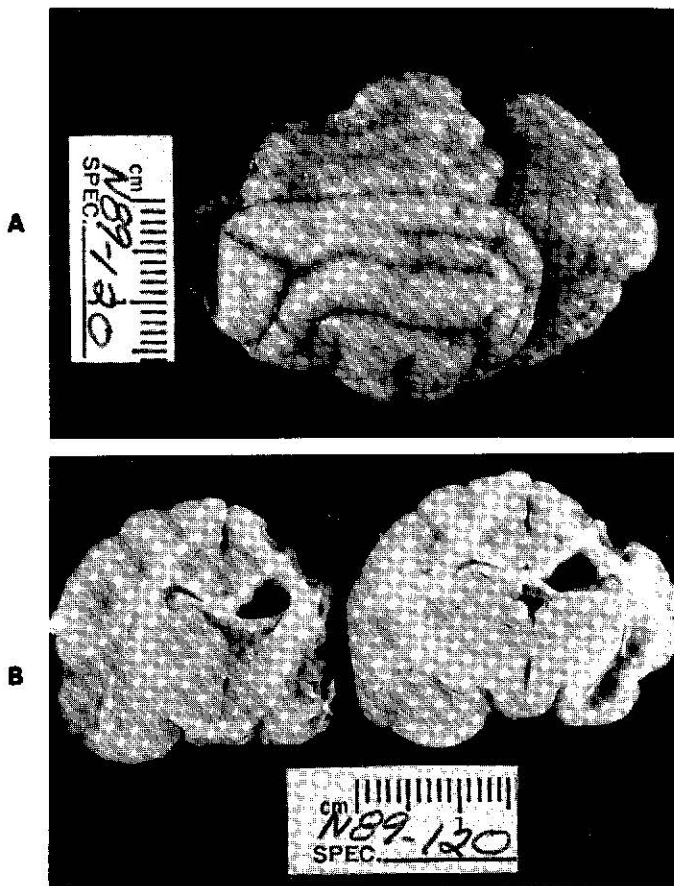


Fig. 5-23. Feline ischemic encephalopathy. **A**, Marked atrophy of right cerebral hemisphere. **B**, Transverse sections show extent of cortical loss and secondary ventricular dilation.

often there is severe loss of the pyriform lobe, amygdala, parahippocampal gyrus, claustrum, internal capsule, and the subcortical white matter.³⁹ Extensive tissue loss will result in some degree of secondary ventricular dilation. In the areas of necrosis, cavitations are often found. Lesions predominate in, but are not limited to, the territory of the middle cerebral artery. Thus necrosis of the hippocampus and the brain stem can be found, and in one case the major lesion was cerebellar.³⁸ Microscopically these areas of infarction are mostly ischemic. There is often spectacular involvement of the pyramidal neurons in the hippocampus (Fig. 5-24). In the cerebrum, ischemic neuronal necrosis resulting in intense cytoplasmic eosinophilia and shrunken pyknotic nuclei is more conspicuous than are white matter changes. Infarcted white matter is pallid with small pyknotic glial nuclei; it is sharply demarcated from viable tissue. Early in the clinical course, the limited inflammatory cell response points to the lack of vascularization of the tissue. Neutrophils are the earliest leukocytes to appear, soon to be replaced by monocytes, which are converted to gitter cells. Some siderophages are seen, reflecting local areas of bleeding, and at the margins of chronic cavitated lesions the

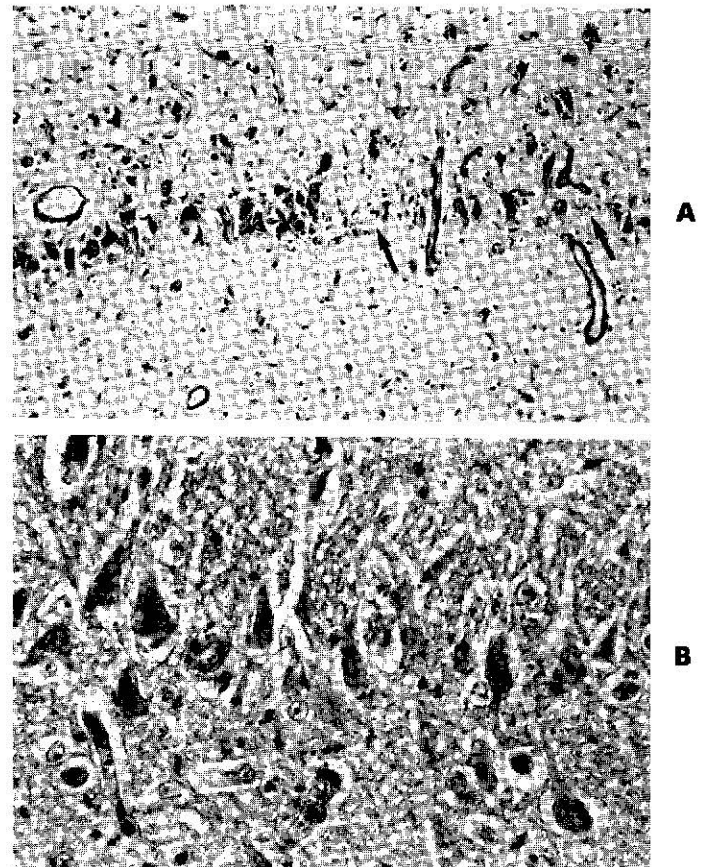


Fig. 5-24. Feline ischemic encephalopathy. **A**, Areas of neuronal loss (arrows) and neovascularization in hippocampus. (Luxol fast blue, cresyl echt violet, $\times 140$.) **B**, Ischemic pyramidal neurons. (LFBCEV, $\times 350$.)

occasional lymphocytic perivascular cuff will be encountered. In some cases, a meningeal influx of eosinophils is noted. Vascular lesions are typically not found, although spectacular thrombosis of the middle cerebral artery was seen in one of our cases.

An examination of the heart for evidence of an underlying cardiomyopathy in cats with this cerebral infarction syndrome has not been rewarding. The pathogenesis remains to be explained. A peak in the number of cases in the summer months could be explained by an insect-transmitted microfiliid, but intravascular parasites have not been found. Some of the brain stem lesions that accompany the cerebral infarction resemble parasite tract injury, and a few cases have shown an eosinophilic leukocyte response. Thus we are of the opinion that a parasitic basis is possible, perhaps larvae of *Cuterebra*, although how this would perturb vascular perfusion is entirely unknown. One hypothesis would be that cerebral ischemia is caused by vasospasm, resulting from hemorrhage⁴⁰ caused by the migrating parasite. In support of this hypothesis incriminating a parasite is the observation that cerebrocortical ischemic degeneration is often found in cat brains with typical parasitic tract lesions that

have focal areas of necrosis and hemorrhage. These necrotic areas abound with macrophages and often contain a few eosinophils. On five or six occasions, we have recovered a *Cuterebra* larva from the cranial cavity in cases of feline ischemic encephalopathy. Supportive of a role for *Cuterebra* is that feline ischemic encephalopathy has not been recognized in Australia and New Zealand where this parasite is not found. Occasionally the lesions of feline ischemic encephalopathy are accompanied by an extensive degeneration of the ependymal lining of the ventricular system with minimal inflammatory response or by subpial white matter degeneration and astrocytosis in the spinal cord. This lesion appears to be toxic in nature.

Cerebrovascular accidents

A cerebrovascular accident or stroke is a suddenly developing focal neurological deficit resulting from an intracranial vascular event.⁴ In humans, factors that predispose to strokes include arteriosclerosis and chronic hypertension, resulting in brain injury that may be focal ischemia (most common) or intracerebral or subarachnoid hemorrhage. What may be comparable in the dog are cases of acute cerebral hemorrhage that have been recognized sporadically. Atherogenic vascular degeneration is uncommon in the dog but where encountered is a consequence of hypothyroidism. Thyroid failure (commonly lymphocytic thyroiditis) results in hypercholesterolemia and spectacular lipid and cholesterol deposits in medium-sized arteries and arterioles in multiple organs. The thickened, yellowed, pipe-like vessels are grossly apparent. In such cases, neurological complications are rare but have been recorded.⁴¹ Systemic hypertension is now recognized in the dog⁴² and may prove to be contributory. Most recorded cases of cerebral hemorrhage in the dog are single instances,⁴³ although one report of 17 cases has been published.⁴⁴ This latter study showed an average age of 11.5 years with no sex or breed predisposition. Associated factors included atherosclerosis (with thyroid atrophy), sepsis, coagulopathy, primary or metastatic brain tumor, and vascular malformation; some were idiopathic. All had an acute onset of neurological deficits, most commonly referable to the rostral fossa. Presenting signs included seizures, circling, stupor, or visual loss. A CSF examination may show an elevation of protein, and the focal hemorrhage can be detected by scintigraphy⁴³ or other imaging procedures. If the seizure activity can be controlled, there is a reasonable probability that the dog can accommodate for the lesion.

In those that are euthanized or succumb because of severe brain swelling, most hemorrhages are single and located in the cerebrum, often in the area of the hippocampus-amygdala (Fig. 5-25). Microscopically, the most acute cases reveal fresh hemorrhage and acute neuronal necrosis. This is slowly removed by macrophages, which are heavily laden with hemosiderin or lipid products. With time, a cystic cavity lined by fibrillary astrocytes will remain. On rare

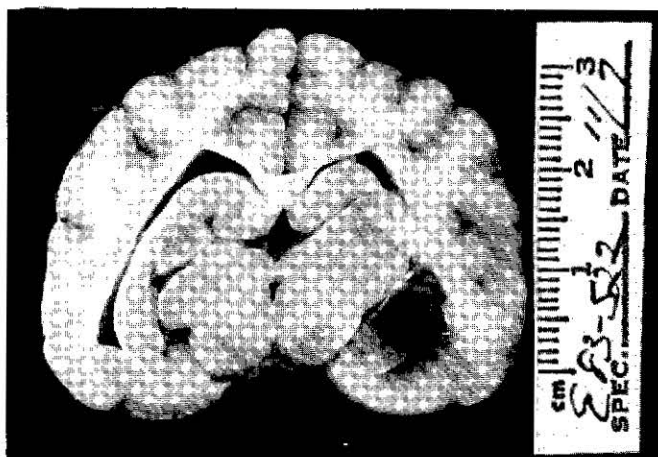


Fig. 5-25. Cerebrovascular accident, dog.

occasions, an aberrant parasite, such as *Dirofilaria immitis*, will migrate to the cerebral circulation and produce cerebral infarction;⁴⁵ *D. immitis* larvae have been associated with acute infarction in one dog.⁴⁶

We have encountered sporadic cases of cerebellar infarction in the dog⁴⁷ and cerebral infarction in other species.⁴⁸ Hemorrhagic infarcts have been associated with cerebral venous thrombosis in a dog.⁴⁹ Cerebral and dural venous thrombosis in four **rhesus monkeys** was associated with patchy areas of perivenular demyelination in the centrum semiovale and internal capsule.⁵⁰ Chronic edema of white matter can result in slow myelin destruction.⁵¹

Spontaneous cerebrovascular atherosclerosis and associated cerebral infarction has been observed in 8- to 12-year-old **swine**.⁵²

Seizures and cerebral necrosis

An area of neuropathology that has been (and remains) a diagnostic difficulty is the relationship between seizures and brain injury. In humans, it is an accepted principle that severe seizure activity causes ischemic neuronal necrosis in certain areas of predilection, such as the neocortex, hippocampus, and amygdala.^{23,53} Furthermore, in a number of rodent and primate models of human epilepsy employing pharmacologically-induced seizure disorders, similar brain changes have been induced. The relative importance of systemic factors (hypotension, pyrexia, hypoxia, hypoglycemia) versus local effects (neuronal hyperactivity) in producing seizure-induced neuronal necrosis has long been debated. In humans, the term epileptic brain damage encompasses the lesions found in chronic epileptic patients and those occurring after an episode of severe seizures with status epilepticus; although microscopically similar, these changes may well differ in their pathogenesis.⁵⁴ In contrast to the foregoing, the association between spontaneous sei-

zure disorders and brain injury in domestic animals is much less clearly established.

Seizure disorders can be divided into two categories: (1) primary or idiopathic, in which an underlying CNS disorder cannot be identified and a genetic basis is sometimes suspected;⁵⁵ and (2) secondary or symptomatic, where there is an associated brain disease such as hydrocephalus, a viral encephalitis, or a neoplasm.

Palmer⁵⁶ recorded his neuropathological examinations of 40 dogs with primary or secondary seizure disorders. Of those with idiopathic epilepsy (12 of 40), ischemic neuronal change was not found, and the only microscopic changes observed (in some cases) were perivascular hemorrhages in the cerebellum. Our experience with idiopathic epilepsy is in accord with that of Palmer, and others seem to concur.⁵⁷ However, lesions have been found in seizing Beagle dogs. These dogs are from a colony used to study the long-term effects of low-level ionizing irradiation. Beagles are prone to develop epilepsy,⁵⁵ and seizures are a significant cause of death in both irradiated and control animals. In one series of 68 dogs, 48.5% had classical ischemic neuropathological changes in the brain.⁵⁷ These consisted of astrocytic swelling, ischemic neuronal necrosis, and basophilic incrustations of ischemic neurons. These dogs were on a life-time study, received no therapy for their seizures, and in some cases were in status epilepticus. The neuropathological changes were not accompanied by significant vascular reaction or astrocytosis, raising the question of whether they were a fairly terminal development. However, in an experimental study of hippocampal ischemia, acidophilic neuronal ghost cells could be identified as long as 15 weeks after carotid artery occlusion.⁵⁸ In addition to this comprehensive study, the literature contains only rare case reports of an association between seizures and structural changes in the brain. Bilateral hippocampal necrosis with loss of pyramidal neurons and gliosis was found in a 3.5-year-old Poodle dog that had had episodes of seizures for a few weeks.⁵⁹ Whether this lesion was the cause or the result of the seizures could not be established; the authors' concern was that a prior neurological illness may have impaired the arterial perfusion of the hippocampus. A Shetland sheepdog with a 3-year course of seizures, including periods of status epilepticus, was euthanized. At necropsy, some degree of atrophy of the cerebral hemispheres and parts of the hippocampus were appreciated.²² Microscopically, bilateral and symmetrical neuronal loss, astrocytosis, and neovascularization were found in the cingulate gyrus, frontal lobe, amygdala, hippocampus, and the dorsomedial nucleus of the thalamus.

Although firm data are lacking, the general failure to find morphological changes in the brains of dogs with idiopathic seizure disorders may relate to the innate resistance of the dog to develop such changes, the severity and frequency of the seizure episodes, therapeutic intervention or euthanasia before brain changes have evolved. If seizure-induced isch-

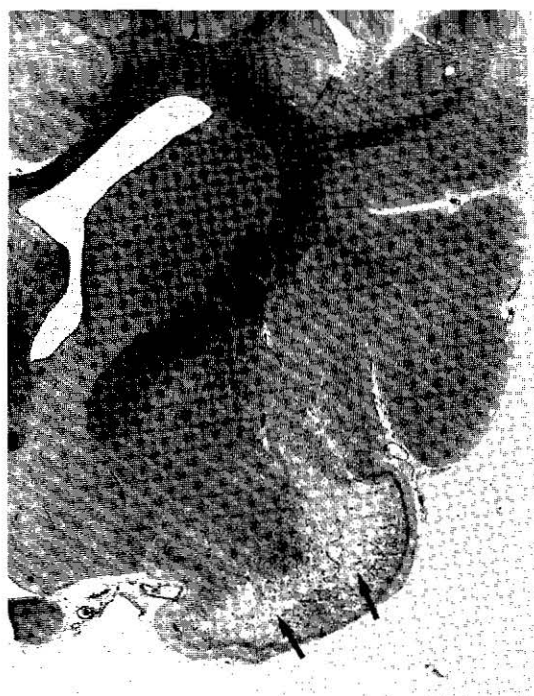


Fig. 5-26. Seizure-associated pyriform lobe necrosis, dog. Cerebrum is rarified and cavitated (arrows). (H&E, $\times 5$.)

emic brain injury is to occur in the dog, it seems more likely to be found in the younger dog than in the mature animal.⁵⁶ This may explain the occasional observation of pyriform lobe and hippocampal necrosis in dogs that have seizures as a result of canine distemper encephalitis. In those cases recorded, more than half were less than 1 year of age.^{60,61}

There are a number of reports of polioencephalomalacia in the dog, more or less affecting neuronal cell populations in the distribution given earlier as that predisposed in hypoxia-ischemia. Seizures of varying severity and duration were common historical factors, but whether this was the cause or the result of the neuronal necrosis could only be conjectured. Lesions of this type involving the amygdala and hippocampus are often associated with altered behavior and, in particular, aggression.⁶² In 15 cases described by Hartley,⁶³ some were secondary in that there was an association with lead or cyanide poisoning, canine distemper infection, or viral hepatitis, although Hartley thought that the association was coincidental. The remainder were idiopathic. Fischer⁶⁴ described severe cavitating lesions of the pyriform lobe (Fig. 5-26), amygdala, hippocampus, and cingulum in 10 dogs with seizures. Some dogs had gastroenteritis that preceded the onset of CNS disease. Of 25 dogs with polioencephalomalacia studied by Braund and Vandeveldt,⁴⁶ the cause of the lesions could not be established in 7. The authors commented that the relationship

between seizures and polioencephalomalacia remains to be clarified as only four of the seven were in status epilepticus.

Hypoglycemia

A number of intrinsic or acquired disorders in animals produce transitory or prolonged hypoglycemia. Constitutional hypoglycemia occurs in some **toy and miniature dog breeds** such as Poodles, Pomeranians, Chihuahuas, and Yorkshire Terriers. Affected pups usually present within the first 6 months of life,⁶⁵ and the disorder can be provoked by fasting.⁶⁶ A transitory hypoglycemia affects active **hunting dogs**, and a more serious form occurs in hypoadrenocorticism (Addison's disease), severe hepatic and renal disease, and glycogen storage diseases.⁶⁷ An important cause of canine hypoglycemia is pancreatic **β -cell tumors**, which result in hyperinsulinism,^{68,69} and a case in a Shetland pony has been described.⁷⁰ Hypoglycemia is also associated with hepatic and other non-pancreatic neoplasms.^{71,72} Neonatal piglets are prone to develop hypoglycemia and seizures if they are deprived of the sow's milk, and hypoglycemia probably occurs in other newborn animals under similar circumstances. Hypoglycemia occurs in ruminants with acetoneuria and pregnancy toxemia. Microscopic changes in the neocortex—neuronal necrosis and astrocytic swelling—have been described in sheep with pregnancy toxemia.⁷³

The clinical signs in hypoglycemic animals may begin with lethargy and dullness that progress to muscular weakness, muscle twitching, seizures, coma, and, if untreated, death.⁷⁴

Studies of the CNS in animals with these syndromes are largely lacking. The neuropathological changes in two dogs with pancreatic islet cell tumors were reported by Krook and Kenney.⁷⁵ Neuronal degeneration was widespread, although largely sparing the hippocampus, which is unusual, given the experience in humans and experimental animals. Several types of injury were recognized, including chromatolysis and ischemic cell change. There were areas of neuronal depletion, sometimes marked by neuronophagia. One dog with a pancreatic islet cell adenoma had extensive, bilateral polioencephalomalacia in the cerebral cortex and basal nuclei.⁴⁶ In puppies that died with **hepatic steatosis**,⁷⁶ four were known to be hypoglycemic, and many had ischemic neuronal changes in the neocortex with reactive blood vessels and gliosis. Neuronal necrosis in hypoglycemia is believed to be mediated by excitotoxins,^{77,78} which may be disseminated in the CSF, resulting in injury to periventricular tissue.⁷⁹

Encephalomalacia following intracarotid injection in horses

Protocol in the practice of venipuncture is particularly important when the point of the exercise is to deliver a medication into the venous circulation. At our institution, students are taught to place a needle in the jugular vein and observe the color and nature of the blood flow before at-

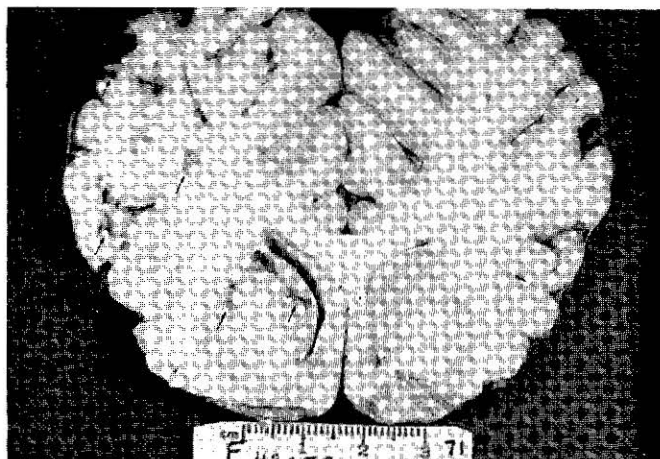


Fig. 5-27. Accidental intracarotid injection, horse. Old cavitated lesions (arrows) affect one side of the brain.

taching a syringe and delivering a drug. If this practice is not followed, horses will occasionally be injected by accident into the carotid artery with substances intended for the jugular vein.⁸⁰ Immediately after the bolus is delivered, the animal will respond violently with headshaking, kicking, and collapse, sometimes with loss of consciousness.⁸¹ Affected horses may recover, although the development of intractable seizures that necessitate euthanasia is a regrettable but common sequel.

Examination of the brains of such cases reveals a characteristic pattern of changes. The hallmark is the asymmetrical distribution of miliary lesions through the rostral brain stem (diencephalon) and cerebrum on the side of the intracarotid injection (Fig. 5-27). This is presumably a consequence of laminar flow of blood in the cerebral arterial circle, resulting in delivery of most of the drug to the ipsilateral side of the brain. In acute cases, the intact brain is congested and mildly swollen, while transverse sections reveal numerous hemorrhagic foci, varying in size from pinpoint up to a few millimeters in diameter, in the distribution given previously. These progressively liquefy and attract macrophages, which are converted into gitter cells. Older lesions are seen as numerous empty cavities attended by a mild astrocytosis at the margins. The drugs in question are invariably promazine tranquilizers, which are presumably cytotoxic in high concentration, resulting in vascular endothelial injury, thrombosis, hemorrhage, and infarction.

Fibrocartilaginous embolic myelopathy

Fibrocartilaginous embolic myelopathy (FCEM) is a peracute neurological syndrome of spinal cord infarction. First described in the dog in the 1970s,⁸²⁻⁸⁴ this disorder is now commonly recognized in dogs and has been recorded sporadically in most other domestic species of animals (Fig. 5-28) and in humans.^{85,86} FCEM particularly affects the

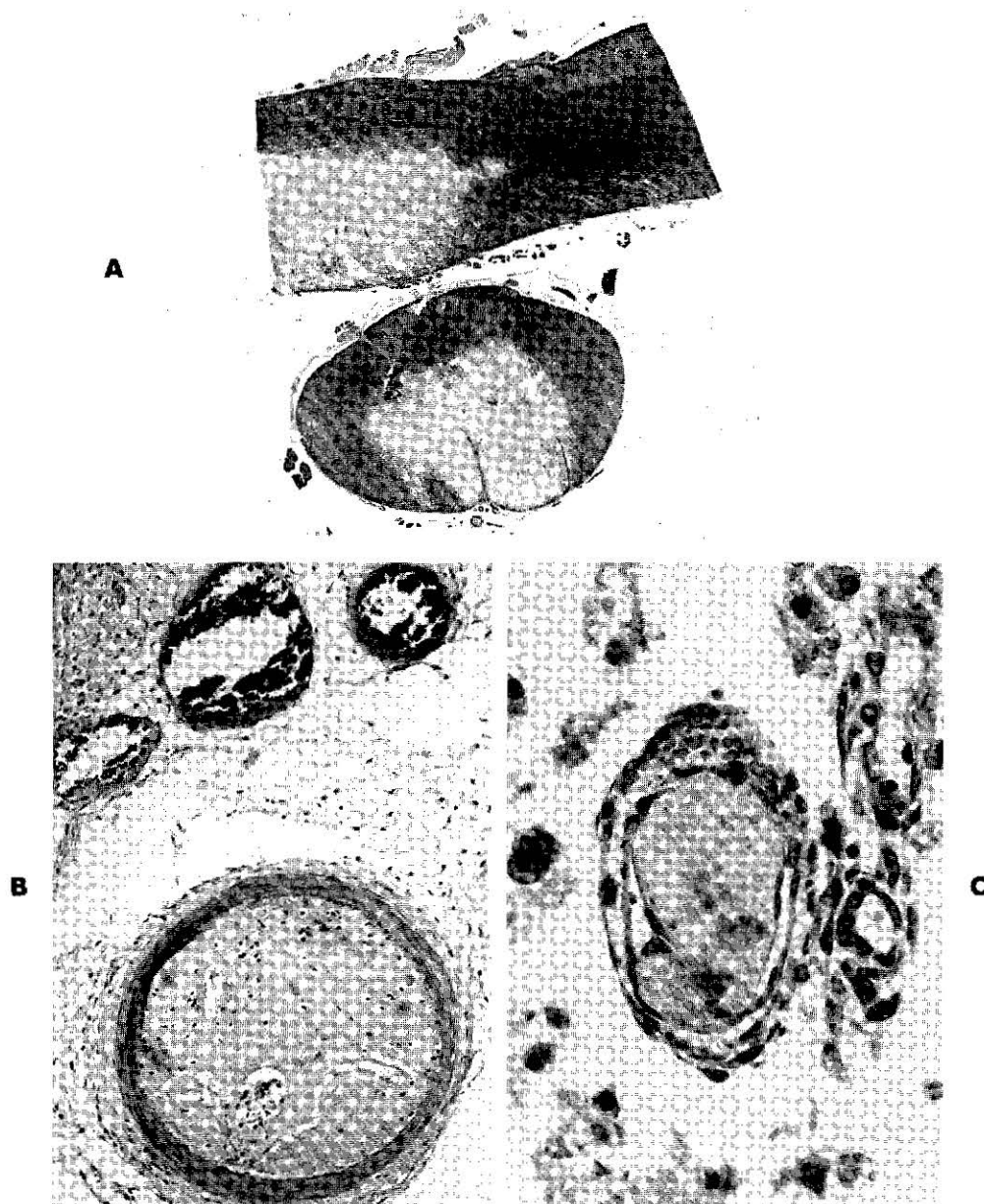


Fig. 5-28. Fibrocartilaginous embolic myelopathy. **A**, Pig. Ischemic spinal cord necrosis. (H&E, $\times 5$.) **B**, Detail of occluded ventral spinal artery (arrowed in **A**). (H&E, $\times 140$.) **C**, Horse with FCEM. Cartilage embolus is covered with endothelial cells. (H&E, $\times 560$.)

larger breeds of **dogs**, but it has not been reported in chondrodystrophic breeds. Cases have been recorded from the first few months of life up to old age, but most commonly the dogs are around 3 to 7 years of age. Clinical deficits develop rapidly, often progressing from apparent lameness to paralysis in a limb or limbs within a few hours. Some affected dogs are found recumbent and unable to rise when first noticed to be unwell. Spinal cord infarction can occur at any point along its length; perhaps 60% of canine cases present with pelvic limb deficits (lesion caudal to T3), with the remainder showing both thoracic and pelvic limb signs

as a result of a more cranial lesion. As FCEM can involve both the gray and white matter of the spinal cord, a combination of lower and upper motor neuron pareses is commonly seen. Furthermore, the degree of paralysis is frequently asymmetrical (left vs. right). Affected dogs are typically bright and alert with a normal sensorium. A lumbosacral infarction that affected the gray matter may present as flaccid paralysis of the pelvic limbs, tail, and anus. These areas are hypalgesic, and the affected limbs show a loss of muscle tone and spinal reflexes. If only the white matter is affected, there is spastic paraplegia. In con-

trast, a cervical spinal cord infarction produces tetraplegia, which would have a LMN quality in the thoracic limb(s) if the lesion involved the cervical intumescence. As these infarcts are frequently asymmetrical, hemiplegia is common. Extensive injury to the cervical lateral funiculus or the gray matter of the cranial thoracic segments will produce an ipsilateral Horner's syndrome.

Typically, plain radiographs of the vertebral column are unrevealing, but a myelogram may suggest the presence of spinal cord swelling. A CSF analysis usually shows albuminocytological dissociation, that is, elevated protein and normal (< 5) cells. In some cases the CSF contains free erythrocytes. A clinical diagnosis of FCEM is made on the basis of the peracute, non-progressive course in the absence of known trauma. In several dogs with this presumptive diagnosis, considerable recovery of function has been recorded,^{84,87} particularly cases with UMN deficits.

In dogs that come to necropsy, the lesion found is an infarct that extends over several spinal cord segments. Grossly, the affected area may be visibly swollen; when the dura is incised, the involved segments may be appreciably discolored (brown) and soft to palpation. The amount of the spinal cord infarcted is most severe at the center of the lesion and tends to taper off in the adjacent cranial and caudal segments. Commonly areas of both gray and white matter are affected, for example, the ventral horn and the adjacent ventral funiculus. Infarction may involve both left and right halves of the spinal cord but is commonly asymmetrical. Areas of infarction may be ischemic, which grossly appear gray, or may be hemorrhagic, which are reddish brown and darken after fixation in formalin. Microscopically, the ischemic infarcts consist initially of pale, structureless tissue with ghosts of neurons, glial cells, or myelinated axons, perhaps with some small blood vessels surviving. The margins tend to be sharp and in a couple of days are marked by a zone of neovascularization and macrophage accumulation. A few polymorphonuclear cells will respond to the necrotic parenchyma also. If the infarct is within a spinal funiculus, there is focal axonal swelling and some spongy ballooning of myelin at its margins. The infarcted tissue liquefies and is filled with a sea of gitter cells; if large enough, it will form a cavity.⁸³ Hemorrhagic infarcts show the same background process amid considerable hemorrhage and edema. If the ventral horn gray matter is infarcted, Wallerian degeneration develops in its neuronal projections in the ventral funiculus and in the ventral spinal roots.

The diagnostic finding in FCEM is the intravascular emboli of fibrocartilage that may totally or partially occlude the affected blood vessel. These emboli are found in leptomeningeal vessels, commonly the ventral spinal artery and vein, and within many intramedullary blood vessels. Some authors have described them only within arteries, some only within veins, and some within both types of vessels. Often the type of vessel occluded cannot be positively stated, particularly if an artery is suspected but an internal elastic

lamina cannot be identified and the vessel wall (tunica media) is attenuated by the occluding material.

The embolic fibrocartilage is identified by its microscopic appearance, sometimes having vague suggestions of chondroid cells within lacunae if not too degenerate. The matrix is grayish in H&E-stained sections, magenta with PAS, tan with PTAH, and blue with Alcian blue stains. In an apparent attempt at organization of this foreign material, its surface is progressively covered by endothelial cells. To produce infarction of the spinal cord parenchyma, which is supplied by branches from a single ventral and paired dorsal spinal arteries, multiple intramedullary tributaries must be occluded. An ischemic infarct will become hemorrhagic if some blood flow continues into the area of injury.

The source of the embolic fibrocartilage and the mode by which it enters the spinal circulation have intrigued clinicians since this disorder was first described in humans. Most investigators believe that the material is derived from the nucleus pulposus of a degenerate intervertebral disk, although the annulus fibrosis⁸² and vertebral growth plate cartilage⁸⁸ have also been suggested as the source. It is intriguing that this disorder does not occur in the chondrodystrophic dog breeds that are most prone to develop intervertebral disk prolapse (Dachshund, Pekingese, French Bulldog). Rather, FCEM occurs more commonly in the larger breeds (St. Bernard, Doberman Pinscher, Labrador Retriever), in which a different, more slowly developing pattern of disk degeneration occurs, which may somehow predispose them to vascular involvement. The status of the intervertebral disks immediately below the area of spinal cord infarction is not always closely evaluated. Where studied, they have sometimes appeared normal, while other cases have shown radiographic or gross pathological evidence of degeneration. In humans, a disk may prolapse laterally into the medullary cavity of a vertebral body, producing a mass known as a Schmorl's node. Potentially this may afford disk material access to the basivertebral veins, if indeed this is the pathogenesis of the embolic process in humans. In dogs, however, Schmorl's nodes are exceptionally uncommon, and so this pathway cannot be invoked. Degenerate disk material has been observed to prolapse dorsolaterally and then rupture and enter the longitudinal internal ventral vertebral venous plexus in the dog. Reflux back to the spinal cord vasculature would then theoretically be possible (during intra-abdominal pressure changes, such as from coughing or straining), but that this would explain all cases of FCEM seems unlikely. The presence of arteriovenous connections has also been invoked, but that they are involved is not known. Hayes and associates⁸⁹ performed a careful study of the intervertebral disks in cases of FCEM and suggested that nucleus pulposus from herniated disks may enter the reactive, newly formed arterial vessels in the annulus fibrosus. From small arteries in the disk, retrograde flow in the radicular artery and then to the spinal cord would need to occur.

The role of trauma in the pathogenesis of FCEM is controversial; overt injury has been associated with FCEM in humans but not the dog. It is recorded that several dogs were exercised a few hours before the onset of clinical signs, which itself may be sufficient trauma to precipitate embolization if the vertebral column is appropriately predisposed. It is yet to be clarified how the presumed intervertebral disk fibrocartilage gains access to the vascular circulation (both the arterial and venous sides) and how such fragments are delivered to the meninges and spinal vessels.

It is of interest that in mature mink with intervertebral disk degeneration, emboli have been observed in the pulmonary arteries.⁹⁰ It is also noteworthy that these mink develop Schmorl's nodes in association with their disk disease. In the other domestic species, we can add little more than that the syndrome has been recorded. There are rare descriptions in **cats**,^{91,92} **horses**,^{93,94} and a **lamb**.⁹⁵ The ovine case is remarkable in several aspects: The lamb was only 1 week old when euthanized, and yet the pathological changes appeared to be at least that old. Further, embolization and infarction spread from the C6 spinal cord segment cranially to the cerebellum. FCEM has been recorded in **swine**, including 45- and 62-day-old weaners⁹⁶ and an adult sow with a degenerate L5-L6 intervertebral disk and an associated L5 vertebral body fracture.⁹⁸ Through the courtesy of Dr. E. Waters (University of Saskatchewan), we have studied a case of FCEM in a 2-year-old Landrace pig. There was ischemic necrosis of the lumbar spinal cord and of the lumbar axial muscles; in both sites, arteries contained fibrocartilage. It is hard to imagine how intervertebral disk fibrocartilage would gain access to the lumbar spinal arteries that supply both the spinal cord and axial muscles, which raises the possibility that this embolic material is not derived from degenerate disks—but, if not, from where?

Traumatic feline ischemic myelopathy

Three cats have been studied at autopsy at varying intervals following an unobserved acute onset of pelvic limb paralysis. They were found dragging their pelvic limbs. On examination, all three had extensive lower motor neuron paralysis and analgesia of the tail, anus and perineum, pelvic limbs, and caudal abdominal wall. All three had evidence of abdominal injury that varied from mild to severe sublumbar retroperitoneal hemorrhage, to avulsion of one kidney and peritoneal hemorrhage. No vertebral column injuries were observed on radiographs or at autopsy.

In two cats, extensive areas of ischemic necrosis-infarction were present in the lumbar epaxial muscles. There were no gross lesions in the vertebral canal or on the external surface of the spinal cord. On transverse sections, varying degrees of the central portion of the spinal cord from L2 through the caudal segments were slightly discolored gray and soft. On microscopic examination, this related to a severe ischemic degeneration of all of the ventral gray columns bilaterally, including the central canal and associated gray and white matter, all or the basal parts of the dorsal gray columns, and usually the immediately adjacent white matter. The cranial extent of the lesion varied from L1 to L3 and was usually asymmetrical at that level. Early lesions showed acute ischemic necrosis with infiltration of macrophages. Older lesions showed extensive astrogliosis intermixed with the lipid-laden macrophages.

This lesion is in the distribution of the branches of the ventral spinal artery that pass dorsally in the ventral median fissure and arborize into the gray matter and in the terminal zone of the area supplied by the blood vessels that penetrate from the vascular plexus on the surface of the spinal cord.

Experimentally similar lesions have been produced in laboratory animals by ligating the aorta at the level of the renal arteries, depriving the spinal cord of the blood normally supplied through the spinal branches of the lumbar arteries.⁹⁷

It is our hypothesis that these cats are injured by vehicle tires that run over the abdomen without causing a fracture but seriously contuse the soft tissues, creating vasospasm or thrombosis of the lumbar arteries for a long enough duration (probably more than 45 minutes) to result in permanent degeneration of the part of the spinal cord most vulnerable to ischemia. Branches of the same lumbar arteries also supply the epaxial muscles, where ischemic infarction was also observed.

An **ischemic neuromyopathy** of the pelvic limbs occurs in cats with thromboembolism of the distal aorta. Most cases occur in cats with cardiomyopathy. A similar syndrome occurs in the horse. Because the infarction afflicts the PNS, it is discussed in Chapter 7.

Treatment of life-threatening epistaxis in equine guttural pouch mycosis sometimes involves surgical occlusion of the bleeding vessel, commonly the internal carotid artery. **Infarction of the optic nerve** has been recorded as a complication of this procedure.⁹⁸

References are on page 333.

Intoxications and toxicoinfectious diseases

Animals are exposed to a great variety of poisonous substances. Toxic plants comprise an important group and include both natural vegetation and species cultivated for pasture. A few plants induce changes that mimic the inherited lysosomal storage diseases, and they are discussed in that section of this chapter. There are a bewildering array of man-made noxious substances in the environment: industrial effluents and fumes, heavy metals, automobile and machinery lubricants, antifreeze solutions, disinfectants, herbicides, insecticides, and rodenticides, to name a few. Further, there are neurotoxins of importance produced by bacteria and fungi on pasture plants and stored grains or within the alimentary tract.

The successful diagnosis of a neurotoxic disorder often requires close interaction between the clinician, pathologist-toxicologist, and epidemiologist, and often it taxes the detective skills of them all. This discussion is largely limited to the most important neurotoxicoses that incite some type of diagnostic morphological change in the CNS. Many poisons produce remarkable CNS stimulation (metaldehyde, strychnine) but seem to do so by altering function alone and are the domain of the analytical toxicologist.

LEAD POISONING

Although the poisonous properties of lead salts have been known for at least 2000 years, lead remains an important poison in humans and animals. In the domesticated animal species, lead poisoning is most commonly encountered in cattle and dogs, which may reflect their innate curiosity and indiscriminate eating habits, as well as the sources of lead to which they are exposed. Thus calves and puppies often chew and lick woodwork with old flaking paint, rich in lead, whereas horses, for example, are more commonly chronically poisoned while grazing pastures contaminated by discharge from lead smelters or from inhalation of their fumes.

A considerable list of potential sources of lead can be compiled, and the relative importance of a source varies from case to case of intoxication. Old paints contain a variety of lead salts (sulfate, carbonate, chromate), and many episodes of intoxication are caused by licking or chewing old painted woodwork or peeling, flaking paint. Modern paints have reduced lead but are not lead-free. Lead is found within putty, linoleum, and roofing materials, which often seem attractive delicacies to inquisitive animals. Wild birds may be poisoned by ingesting lead shot in ponds and lakes. Sheep and horses are poisoned if they graze fields contaminated by lead-mining operations or the discharge from smelting. Old batteries are often attractive to cattle, as seem to be other materials containing lead,¹ such as machinery grease, used motor oils, and gasoline, although, of course,

there is a move in some parts toward lead-free gas. Motor vehicle exhaust is a pollutant that affects humans and urban-dwelling animals. In pregnancy, the fetus may be exposed across the placenta, and the effects of prenatal and postnatal lead on the developing CNS, including altered dendritic development, diminished synaptogenesis, and myelin deficits, have been described.²⁻⁵ In humans, prenatal exposure to lead has been associated with impaired cognitive development, resulting, for example, in lowered IQ scores. These effects have been studied in rodents and non-human primates.⁶

In cattle, lead poisoning can be described as clinically acute, subacute, or chronic. The first two expressions are most common, and calves are often affected. Affected animals may be found dead or have a short course of violent activity, bellowing, and continuous seizures, usually terminating in death in a few hours.⁷ In the subacute form, initial diarrhea gives way to constipation and rumen stasis. There is severe depression, blindness and head pressing, and an aimless, staggering gait. The course runs for a few days, and some die from misadventure.

Clinical diagnosis of lead poisoning is supported by the demonstration of anemia with circulating rubricytes and metarubricytes, and erythrocytes with basophilic stippling. Elevated levels of lead in blood may be demonstrated, but in individual cases the elevation may be only marginally above normal levels, whatever "normal" is. Some investigators have demonstrated lead in the urine; if access has been recent, lead may be found in feces.

At necropsy, the observation of known sources of lead such as flakes of paint in the gastrointestinal tract is helpful. Gross changes in the CNS in lead-poisoned cattle are found in some cases, but in all species it is possible to find cases of lead encephalopathy that lack macroscopic and microscopic pathological changes. When present, macroscopic changes vary from mild nonspecific brain swelling to focal yellowish areas of necrosis and even cavitation, most commonly affecting the cerebral cortices.⁸ Microscopically, a range of changes evolve,⁹ and these seem to be consistent, not just in cattle, but for all lead-intoxicated animals. Early lesions are spongiosis and pallor of the cortical neuropil, and prominence of capillary vessels, which are increased in number and have swollen endothelia (Fig. 5-29). Progressively, there is swelling of astrocytes and mild ischemic-type changes of neurons—shrinkage and cytoplasmic eosinophilia. Such cerebrocortical changes are commonly found at the tips of gyri. In some more chronic cases, frank laminar cortical necrosis is found, and patchy foci of malacia occur in nuclear areas in the brain stem.⁸ Mild degenerative changes may be found in liver and kidney, and, in subacute

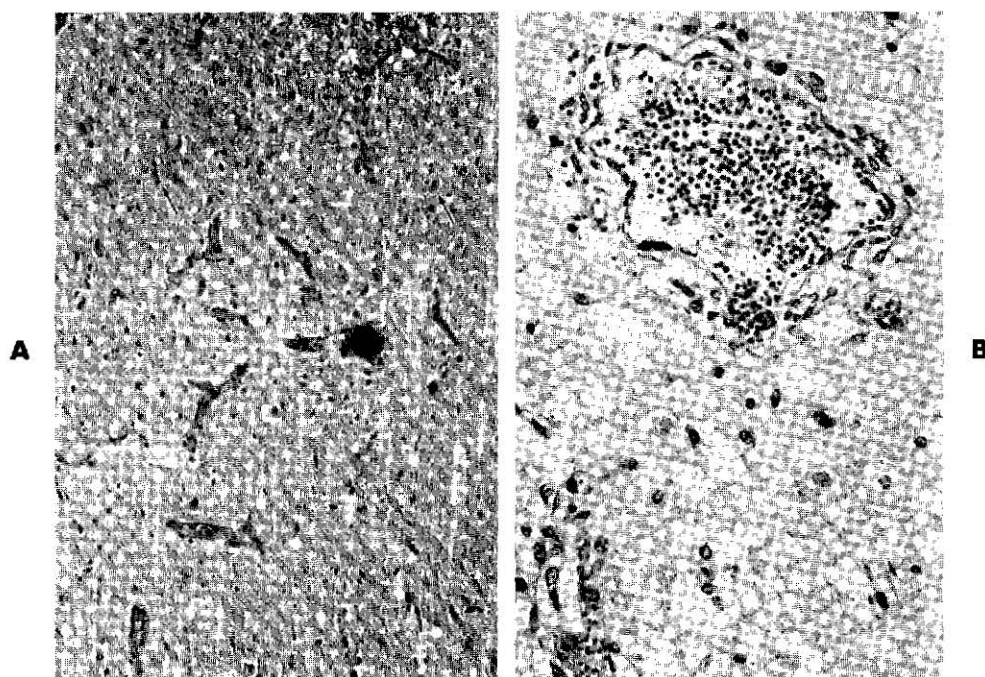


Fig. 5-29. Lead poisoning. **A**, Calf. Degeneration of cerebral cortex, "ischemic" neurons (arrows) and neovascularization. (H&E, $\times 140$.) **B**, Cow. Rarefaction of neuropil in cerebral cortex and slight proliferation of vascular adventitia. (H&E, $\times 350$.)

to chronic cases, a search for acid-fast intranuclear inclusion bodies is worthwhile.

Lead is stored in a number of tissues, and liver and kidney are routinely analyzed. Significant levels also occur in bone, which is a site of long-term storage; during parturition, lead may be mobilized along with bone calcium.¹⁰ Quantities of lead in the brain are not impressive.

Poisoning of **sheep** occurs when they graze where there had previously been lead-mining activities. The signs are subacute. Lead poisoning is uncommonly identified in **cats**¹¹ but is an important cause of morbidity and mortality in **dogs**. Occurring at all ages, lead poisoning in the canine occurs commonly under 12 months of age. Clinical signs relate to gastrointestinal disturbance with abdominal pain, and to neurological changes.^{12,13} Poisoned dogs may be presented showing either manifestation alone or signs of both alimentary and CNS disorder. There is anorexia, vomiting, and sometimes evidence of colic. Neurological disturbances vary from restlessness to hysterical behavior, champing of the jaws, excessive salivation, and seizures.^{14,15} Death may ensue after one or multiple seizures. Blood lead levels are elevated.^{13,16} Erythroid changes are observed¹⁷ as in other species. At necropsy, histopathological changes in the brain are as described previously: swelling of capillary endothelia, proliferation of capillary vessels, sponginess and pallor of the neuropil, mild to focally severe cerebrocortical neuronal degeneration and necrosis of middle and deep laminae, astrocytosis, and microgliosis.¹⁸ Intranuclear acid-fast inclusions may be found in hepatocytes, proximal tubular epi-

thelial cells in the kidney, and the cytoplasm of osteoclasts.¹⁹

Experimental induction of lead poisoning in dogs has allowed the spectrum of CNS changes to be studied. Feeding lead with a high-fat diet apparently enhances solubility and hence intestinal uptake of the salt, resulting in regular induction of neurological disease.²⁰ A small proportion of intoxicated animals have no neuropathological changes.²¹ Lesions are observed most frequently in the neocortex and, with somewhat lesser frequency, the septal area, basal nuclei, diencephalon, and midbrain.²⁰ As in cattle, the tips of cerebrocortical gyri are often affected; an effect, either direct or indirect, on the microvasculature is suspected.

Lead poisoning in **horses** is usually associated with chronic intoxication from contaminated pasture. The neurological effects may be central or peripheral. Experimental intoxications have resulted in seizures and ataxia,²² but spontaneous episodes have also shown colic, muscle weakness, laryngeal hemiplegia, and, in some, inhalation pneumonia.^{23,24} These presumably reflect the well-known toxic effects of lead on the Schwann cell and are discussed in Chapter 7.

Lead poisoning is most common in the bovine and canine species. Young animals are frequently affected, and the reasons for this pattern may be several. Dietary indiscretion in the young may be one factor. However, gastrointestinal absorption is heightened in this age group, and stable lead complexes may be less readily formed in immature growing bones, permitting exposure of other tissues to the lead salts. Most lead that is ingested passes in the feces; in mature

animals, only approximately 2% is absorbed, and it is slowly excreted in bile. Of that retained, over half is deposited in bones and about a quarter in the kidneys. The toxic effects of lead are doubtless many. One well-recognized action is an inhibition of enzymes with free-sulfhydryl groups.¹⁵ This affects heme synthesis, resulting in the circulating immature and stippled erythrocytes that are characteristic of lead poisoning. Urinary levels of δ -aminolevulinic acid, a substrate in porphobilinogen synthesis, may be elevated. The bases for the neurotoxic effects of lead are probably multiple. Some patterns of neuronal injury suggest an effect on blood vessels, leading to the development of ischemic necrosis. Experimentally it has been shown that low levels of lead can modestly elevate blood pressure, and in part this may be a direct vasomotor effect.²⁵ Direct interference with neuronal function may relate to altered Ca^{++} availability, effects on cell enzymes essential for neuronal functioning, and mitochondrial and membrane effects.^{26,27} There is also considerable evidence that astroglia and oligodendroglia are primary targets for lead toxicity.²⁸

Levels of lead in the gastrointestinal contents, liver, kidney, CNS, blood, urine, and hair have been measured for diagnostic purposes. The values vary widely from species to species, and within species there is a considerable range noted if series of published cases are compared. Experimental intoxications have shown that tissue levels of lead do not correlate with the clinical course or the extent of neuropathological changes. Normal animals that reside in or near industrial areas have higher levels of lead in their tissues than animals from other areas. Thus a single value that establishes poisoning cannot be offered, and readers should consult references for the specific species of their interest; the review by Humphreys is recommended.²⁹ As a guide, in cattle, 30 ppm and 10 ppm in the kidney and liver, respectively (wet weight basis), would be acceptable levels to confirm a clinical syndrome compatible with lead poisoning. If only formalin-fixed tissues are available, they can be used for lead analysis.³⁰

References are on page 335.

ARSENIC POISONING

Poisoning with arsenical compounds has traditionally been divided into two categories, caused either by inorganic salts or by the organic arsenicals. The division is useful insofar as either intoxication occurs under separate circumstances and involves different animal populations; pathogenetically, they may be similar.

The inorganic arsenicals, which are endemic causes of poisonings, are those used in dips for the control of ectoparasites on sheep and cattle and sprayed onto fields or orchards for plant parasite control. Poisoning in either case occurs in grazing species and is marked by abdominal pain, depression, diarrhea, and death.

Organoarsenicals have been added to pig food for 40 years to promote growth rate and efficiency of feed utilization (up to 100 ppm) and at approximately 250 to 400

ppm (for a few days) to treat swine dysentery. Episodes of poisoning are common, resulting from errors in the proprietary preparation of the additive, substitution of one arsenical with another more toxic compound,¹ or in miscalculation in their incorporation into home-mixed feeds. Sometimes excessive arsenicals have been added to creep feed intentionally, but unfortunately 50 times the recommended level is not 50 times as valuable. Pigs that are somewhat dehydrated—whether from a restricted water supply, enteric disease resulting in diarrhea, or whatever—are more susceptible to the toxic effects of these compounds.

Arsanilic acid (*p*-amino-benzenearsonic acid) has perhaps been used most widely and is of relatively low toxicity. In experimental studies, levels in the feed between 611 and 2000 ppm resulted in disease in a dose-related fashion. Affected pigs developed a coarse head tremor and were wide-eyed and apprehensive. A progressively severe ataxia of all limbs and paraparesis rapidly followed, accompanied by the development of blindness.² The visual system has been investigated in intoxicated pigs;³ electroretinograms were recordable but not visually evoked responses.

Affected pigs prefer to remain recumbent and, if forced to move, have an ataxic, stumbling gait and frequently fall. In a separate episode where 8000 ppm had accidentally been fed to young pigs, ataxia was evident after 2.5 days and progressed, despite withdrawal of the incriminated feed.⁴ However, at lower levels of intoxication, many piglets clinically improve if the feed is changed.

Neuropathological changes (Fig. 5-30) are degeneration in the optic nerves and tracts without other CNS alterations.² Wallerian degeneration, with abundant myelin ellipsoids containing myelinophages, is found in the peripheral nerves. Elevated arsenic levels are found in the liver, kidney, and urine.

A second organoarsenical similarly used in swine feed as an additive is 3-nitro-4-hydroxyphenylarsonic acid ("3-nitro"). It is more toxic and so is recommended at lower levels. Clinically and pathologically, poisoning of young growing pigs with 3-nitro differs from that induced by arsanilic acid. Episodes are often produced only by stress,⁵ such as moving animals to a new pen or by forced exercise. The disorder begins with generalized muscle tremors often accompanied by high-pitched squealing.¹ The trembling progressively worsens, leading to sternal recumbency, and one or two may die. Some use their snout to retain their balance and remain standing. When they are recumbent, the tremors diminish and stop. Ataxia with paraparesis or paraplegia develops in some intoxicated animals a few days later. Blindness is not a feature of the syndrome.

The neuropathology has been studied by Kennedy and others⁶ in experimentally intoxicated pigs. There is a diffuse myelopathy, first evident in the dorsal funiculus (particularly the fasciculus gracilis) at the level of the cervical spinal cord. Subsequently, involvement of the lateral and ventral funiculi, first at the lumbar segments, is evident; this pattern suggests a distal axonopathy. There is with progres-

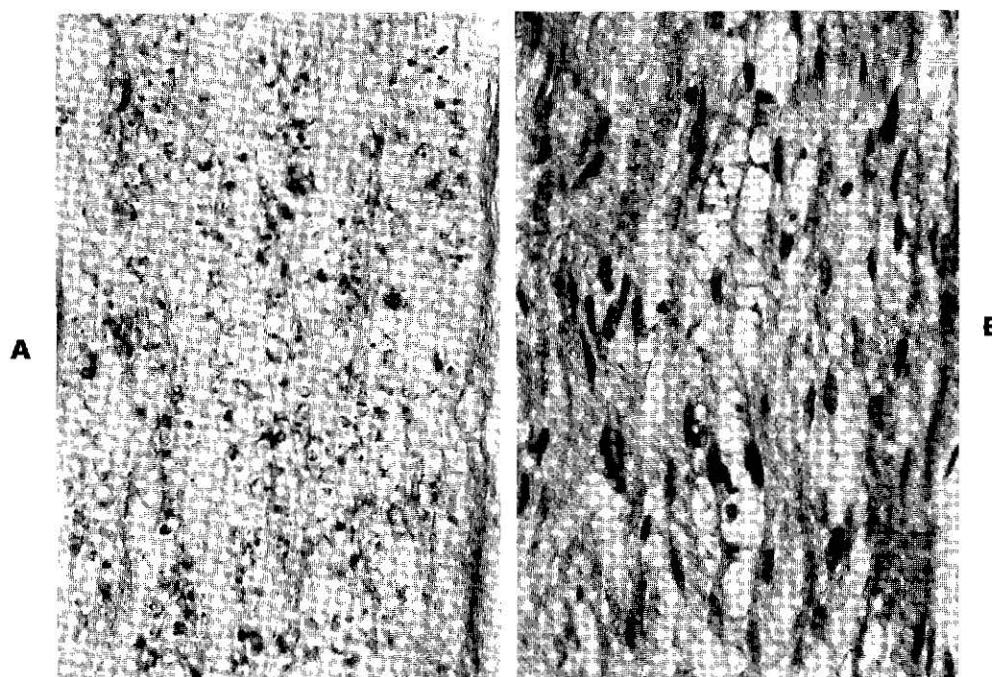


Fig. 5-30. Arsenic poisoning, pig. **A**, Severe fragmentation of myelin in optic nerve. (Myelin stain, $\times 560$.) **B**, Wallerian degeneration in peripheral nerve. (H&E, $\times 560$.)

sion a widespread degeneration in the spinal cord with a reactive astrocytosis. Lesions of the optic nerves and peripheral nerves develop more slowly and are relatively mild and patchy, compared to changes throughout the spinal cord. The clinical expression of 3-nitro intoxication, which consists of seizures precipitated by exercise or by other means, is difficult to relate to the neuropathological findings.

References are on page 336.

MERCURY POISONING

Discharge of industrial wastes into lakes and rivers has introduced mercury into the food chain via various species of fish. Their consumption has poisoned humans and animals, perhaps most widely known at Minamata Bay in Japan.

The mercurial compounds with which we are concerned are the organic salts. As is common in the field of toxicology, the target tissues affected and the disease course produced by organic and inorganic compounds are quite different. The mercurials of importance in veterinary medicine are the alkylmercurial fungicides, such as methylmercury hydroxide, used to control fungal growth on seed grains. Intoxication occurs in pigs and sometimes cattle; the signs are neurological and typically have an abrupt onset, some period after exposure to the treated grain. The clinical course may result in death in a few days. Clinical signs of organic mercury intoxication in **pigs** occur 2 weeks or later after ingestion, depending upon the dose. There is diminished

food consumption, marked weakness, and dullness. Affected pigs have a swaying, ataxic pelvic limb gait and knuckling of the front fetlocks, which progress to recumbency.¹⁻³ Cortical blindness and a semicomatose state (with uremia) may last for days, with aimless wandering or paralysis and intermittent paddling seizures.

At necropsy, there is evidence of nephrosis with swollen kidneys. The cerebral cortices of the brain are bilaterally pale, and microscopic examination reveals acidophilic ischemic neuronal change, particularly of the middle and deep laminae. Reactive astrocytes and microglial cells accompany the neuronal necrosis, as does some capillary proliferation, and a few mononuclear cells are found in the proximate leptomeninges. Necrotic neurons are dark and shrunken and undergo neuronophagia,³ and the neuronal depletion imparts a vacuolated appearance to the cortex. The corona radiata is edematous. Fibrinoid necrosis of leptomeningeal arteries in both brain and spinal cord is characteristic of alkylmercurial poisoning; there is necrosis of the tunica media, loss of endothelial cells, and a fibrinous effusion, admixed with a few mononuclear cells, in the adventitia. Scattered foci of malacia, neuronal degeneration, or spheroids are to be found in the basal nuclei and brain stem. In pigs, a sensory neuropathy with Wallerian degeneration² occurs in chronic cases.

Organomercury poisoning in **cattle** also follows some weeks after exposure. There is sudden onset of ataxia⁴ progressing to seizures, coma with renal failure, and death. Cardiac arrhythmias may follow injury to the Purkinje net-

work. Changes at necropsy resemble those described for the pig. The cerebral hemispheres are soft, and the brain may be herniated. Histological findings are of nephrosis, cardiac Purkinje fiber degeneration, ischemic neuronal necrosis, and fibrinoid leptomeningeal arterial degeneration. In cattle, there is more striking necrosis of cerebellar granule cell neurons and loss of cerebellar Purkinje neurons from the tips of the folia.

Intoxication in **cats** follows the consumption of contaminated fish, whereas **dogs** are more often secondary cases, having been fed on mercury-poisoned pigs. Farm dogs may be poisoned by eating grain treated with mercurial fungicides. In cats, there is anorexia, a crouched ataxic-hypermetric gait, a fine head tremor, bunny hopping (perhaps an indication of weakness), and knuckling of the paw, demonstrating proprioceptive deficits.^{5,6} Poisoned cats may be blind and seizure. The pathological changes are of neuronal degeneration in the cerebral and cerebellar cortices and spongiosis of the molecular layer of the cerebellum. Wallerian degeneration is present in the spinal cord in poisoned cats⁶ and probably other species. That in the dorsal column may be secondary to spinal ganglion injury, whereas corticospinal tract involvement may follow primary cerebrocortical damage. Experimentally intoxicated dogs⁷ and a horse⁸ have shown similar clinical and neuropathological changes.

At necropsy, mercury can be detected in several organs, including the liver, kidney, muscle, and brain. Levels can also be measured in plasma and erythrocytes, but hair may be the preferable specimen with which to make a diagnosis during life.⁹

Alkylmercurials appear to produce neuronal damage by direct toxicity, which may include changes to membrane-associated proteins, protein precipitation, and enzyme inhibition. Vascular degeneration may add a secondary ischemic component to the cerebral injury.¹

References are on page 336.

SALT POISONING

In domestic animals, direct salt poisoning due to the ingestion of large quantities of sodium chloride is quite uncommon. Indirect poisoning, involving an imbalance of salt intake and the availability of pure water, occurs much more commonly; it occurs in swine and poultry with some frequency and sporadically in sheep and cattle.

Indirect salt poisoning is a neurological disorder seen most commonly in **pigs**, usually around 1 to 4 months of age.¹ Swine may be particularly susceptible because of the relatively high load of salt in their diet. This can be tolerated if pure and unlimited supplies of water are always available. Poisoning occurs typically when access to water is limited or totally lacking, such as due to blocking of water lines or freezing of troughs. Clinical signs often develop when unlimited water is made available again. Hence affected swine often initially suffer a period of water deprivation but suc-

cumb following a bout of excessive water consumption (water intoxication).² Thus the designation of this syndrome as salt poisoning, water deprivation, or water intoxication is a moot point.

Clinically, a range of neurological signs may be seen. Sometimes affected pigs have repeated seizures, but this is not invariable. There is depression, simply indicated by the lack of squealing upon handling and restraint. Bumping into objects is due to cortical blindness, and affected pigs may wander aimlessly and head press when encountering resistance. The latter may reflect elevated intracranial pressure from cerebral edema. The typical seizures that have been described² begin with a twitching of facial muscles, jerking upward motions of the head, retropulsion to a dog-sitting position, falling to one side, and paddling with the limbs. Affected pigs have elevated serum and CSF sodium levels.

At necropsy, there is mild to moderate cerebral edema. Microscopically, two characteristic changes are identified (Fig. 5-31). One is a laminar pattern of cerebrocortical necrosis, mostly in the dorsolateral cortex,³ which begins as rarefaction of the neuropil and capillary neovascularization and progresses to neuronal necrosis, particularly of middle laminae; neuronal changes are of the energy-deprivation type. Advanced lesions are cavitated areas of malacia filled with gitter cells. Second, there is a leptomeningeal and perivascular influx with eosinophils in the cerebral cortices. A mixture of both reactions is most common, but either alone may be encountered.

The pathogenesis remains unclear. Eosinophilia of the cerebral cortices seems to follow elevated levels of the Na ion, and similar changes can be induced in swine with other sodium salts.⁴ How and why sodium induces a meningo-cerebral eosinophilia is unknown. The degenerative change is identical to that seen in other forms of energy deprivation (hypoxia, thiamine deficiency), save that other gray matter areas predisposed to such metabolic stresses (e.g., the caudal colliculi) are not affected in salt poisoning; this speaks for a more selective cerebrocortical insult. Elevated CNS salt levels presumably incite cerebral edema, once water is made available again and affected animals, which are thirsty, over-indulge. Rapid rehydration of the dehydrated brain promotes seizures.⁵ Elevated blood levels of salt can be cleared with the ensuing natriuresis, but that within the neuraxis may be more refractory to rapid clearance. Hence, in summary, it seems that the sodium ion imbalance incites the tissue eosinophilia, and the water imbalance ultimately precipitates the laminar cortical necrosis.

In **cattle**, a clinically similar syndrome may follow an excess of salt in the diet in the absence of fresh water,^{6,7} such has occurred in veal calves exclusively fed formula-milk rations, and also in children. In a few circumstances, salty water has been implicated; other episodes have followed the normal dietary salt-water deprivation scenario. Hyponatremia and neurological disease developed in calves undergoing therapy for neonatal diarrhea as a result of im-

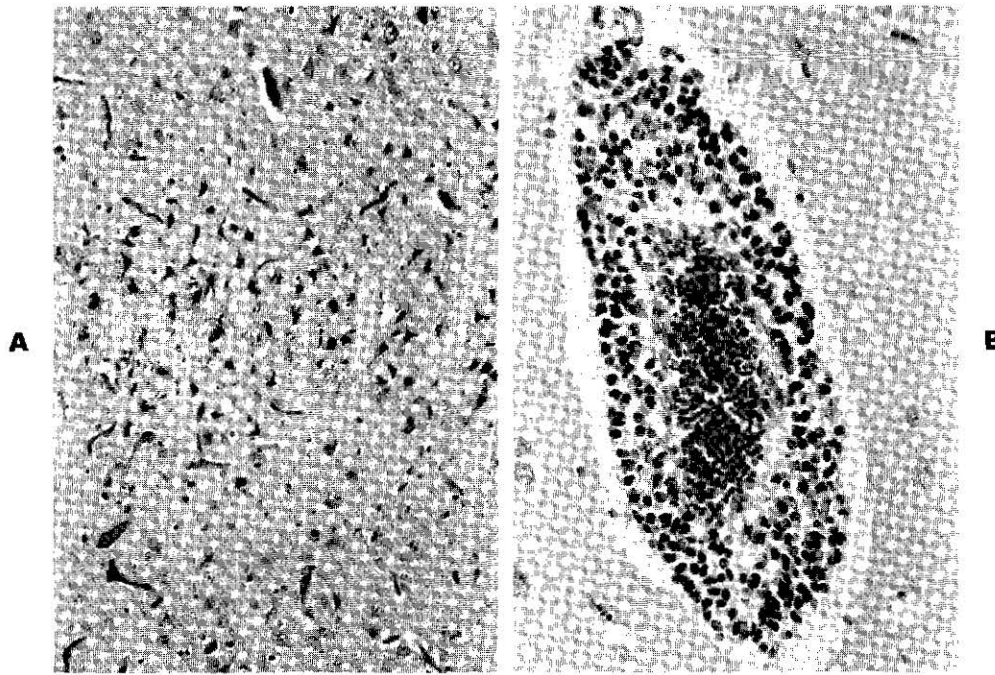


Fig. 5-31. Salt poisoning/water deprivation, pig. **A**, Laminar neuronal necrosis in cerebral cortex. (H&E, $\times 140$.) **B**, Perivascular cuff of eosinophils. (H&E, $\times 350$.)

proper mixing of oral electrolyte solutions.⁸ Affected cattle are depressed and weak and have muscle spasms. Their gait is staggering and ataxic, and they knuckle at the fetlocks. Sometimes hyperesthesia and aggressiveness is seen, and some affected cattle wander aimlessly, apparently blind.⁹ Terminally, recumbency and seizures ensue. Pathological changes, depending upon the clinical course, vary from nil to cerebral edema to cerebral malacia. Epidemiologically, clinically, and pathologically similar episodes are reported in sheep.¹⁰

Hypernatremia in small animals due to adipsia¹¹ may cause lethargy and circling propulsively, but it is not associated with cerebrocortical necrosis. The adipsia may result from defective hypothalamic osmoreceptors.

References are on page 336.

DELAYED ORGANOPHOSPHATE POISONING

The acute clinical effects of poisoning by organophosphates, including miosis, increased salivation, sweating, diarrhea, and muscle fasciculations are well recognized. These signs are due to the inhibition of acetylcholinesterase enzymes, leading to acetylcholine accumulation and (among other effects) parasympathetic overstimulation. In humans and animals, however, many episodes of poisoning with organophosphate compounds have produced a delayed paralytic syndrome, associated with a distal axonopathy.¹ Such have followed accidental contamination of pasture or other foodstuffs with transmission or lubricant oils that contain these esters. Other "industrial" sources are gasoline addi-

tives and plasticizers, while pesticides and anthelmintics, commonly employed in farm animal medicine, are also incriminated. Contamination of illicit drink with organophosphates affected thousands of people in 1930.

Episodes in **sheep** and **pigs** have followed the oral administration of organophosphate anthelmintic compounds,^{2,3} often at recommended levels. **Cattle** and pigs have also been poisoned by organophosphates (usually insecticides) applied to the skin,^{4,5} and episodes in cattle and sheep have followed contamination of feed.^{6,7} Several experimental studies in these species have also been reported.^{6,8,9}

The clinical signs of delayed organophosphate toxicity are manifest some weeks (approximately 1 to 4) to a few months after exposure, depending on the particular compound, dose, frequency of exposure, and recipient. Suffolk sheep, which have low levels of plasma arylesterase activity (which can hydrolyze the organophosphate esters), have an inherited predisposition to this neurotoxicity,^{9,10} and paralysis is seen in younger animals than in high-esterase-level sheep. The onset of clinical disease may be abrupt or slowly progressive over a few days. In all animals it is typified by knuckling of the pelvic limbs and a swaying, ataxic, pelvic limb gait; this commonly progresses to paraplegia. Affected animals adopt a dog-sitting posture or drag themselves along by their thoracic limbs, which may be less severely affected, although some animals are tetraparetic and recumbent. A few animals, less affected, remain ambulatory although paraparetic; they will stabilize with residual deficits. In addition to these signs, cattle may develop marked dyspnea.

The pathological changes are microscopic and most pronounced in the spinal cord and caudal brain stem. Their bilaterally symmetrical distribution follows specific tracts that contain long, large-diameter ascending and descending axonal projections. Thus in the cranial cervical segments, myelin ellipsoids and axonal fragmentation are found with greatest density in the dorsal columns (especially fasciculus gracilis) and dorsal superficial sections of the lateral funiculi (dorsal spinocerebellar tracts). These changes, which incite a phagocytosis of the white matter debris and an astrogliosis, are also especially conspicuous in lumbar segments medially in the ventral funiculi and in the deep lateral funiculi.^{2,7} On some occasions, the pattern of fiber involvement does not conform to a distal axonopathy, suggesting lesions in much more proximal portions of axons.⁴ Chromatolysis is seen in scattered neurons in the brain stem and spinal cord, perhaps also attesting to injury to proximal axonal segments. The topography of this axonopathy is nicely mapped by the regressive Nauta-Gygax technique (Fig. 5-32), which selectively impregnates the granular fragments of axonal debris.^{4,7} Degeneration of preterminal fibers in the spinal gray matter, particularly the medial part of the ventral horn and zona intermedia, is also found. Scattered axonal spheroids are found in the medullary nuclei and dorsal gray columns of the spinal cord. Ultrastructural examination is a study of Wallerian degeneration;⁷ neurons in the spinal ganglia react with neurofilament accumulation or by hypertrophy of their granular endoplasmic reticulum.¹¹

The central (and peripheral) pathology of experimental organophosphate toxicity has been extensively studied (often in chickens¹²) and conforms broadly to Cavanagh's concept of a dying-back neuropathy. However, teased-fiber studies of intoxicated cats^{13,14} showed that the earliest nerve fiber degeneration, although distal, is subterminal. At this focal point, the axon is effectively transected and subsequently undergoes orthograde Wallerian degeneration to its termination; degeneration may also progress proximally, toward the cell body. The delayed neurotoxic effects of organophosphates are not constrained within the CNS, and involvement of peripheral fibers is to be anticipated. In foals, laryngeal paralysis associated with Wallerian degeneration of the (long) recurrent laryngeal nerves has been associated with haloxon administration.¹⁵ Similar laryngeal paralysis and neuropathy occurred in adult horses inadvertently exposed to oral trichlorfon.¹⁶ A further effect, seen in pregnant swine treated with trichlorfon, is the induction of congenital cerebellar hypoplasia in the litter.^{17,18}

The mechanism whereby these organophosphate esters incite a delayed axonopathy has been a field of active study. Inhibition of acetyl-cholinesterase or of pseudocholinesterase enzymes seems not to hold the answer to delayed toxicity. Research has focused on a target protein, found in neurons and some other cells,¹⁹ and designated as neurotoxic esterase or neuropathy target esterase;²⁰ a physiological role for this membrane-bound enzyme is not established.¹ Neural



Fig. 5-32. Delayed organophosphate poisoning, sheep. Degeneration of axons in lumbar spinal cord is seen as clumped fragments. (Nauta-Gygax, $\times 560$.)

toxicity is believed to (somehow) follow phosphorylation and subsequent "aging" of the protein, the latter resulting in a side-chain loss with a subsequent residual (acidic) charge at the active site. Other compounds that inhibit the neurotoxic esterase but do not undergo "aging" do not incite paralysis. How these biochemical changes result in the observed clinical and pathological alterations remains to be established.

References are on page 336.

CHLORINATED HYDROCARBON INSECTICIDE POISONING

A variety of chlorinated hydrocarbon insecticides have been used as sprays or dips to control ectoparasites on **pigs, cattle, sheep, and goats**; dieldrin, toxaphene, and lindane are three such examples. Use of these compounds has now diminished because of their known persistence in animal tissues (particularly in fat depots) and in the environment.

If exposure occurs by the alimentary route, intoxication may be seen in 30 minutes, as occurred in swine fed from a contaminated concrete floor.¹ Percutaneous absorption produces a somewhat more delayed response. The chlorinated hydrocarbons are CNS stimulants, and the characteristic clinical feature is episodic seizures.^{2,3} These may be accompanied by salivating, champing of the jaws, vomiting, ataxia, and muscle tremors. Death may occur within a few hours of the onset of clinical signs, although treatment of percutaneous poisoning with warm washes may be successful.⁴

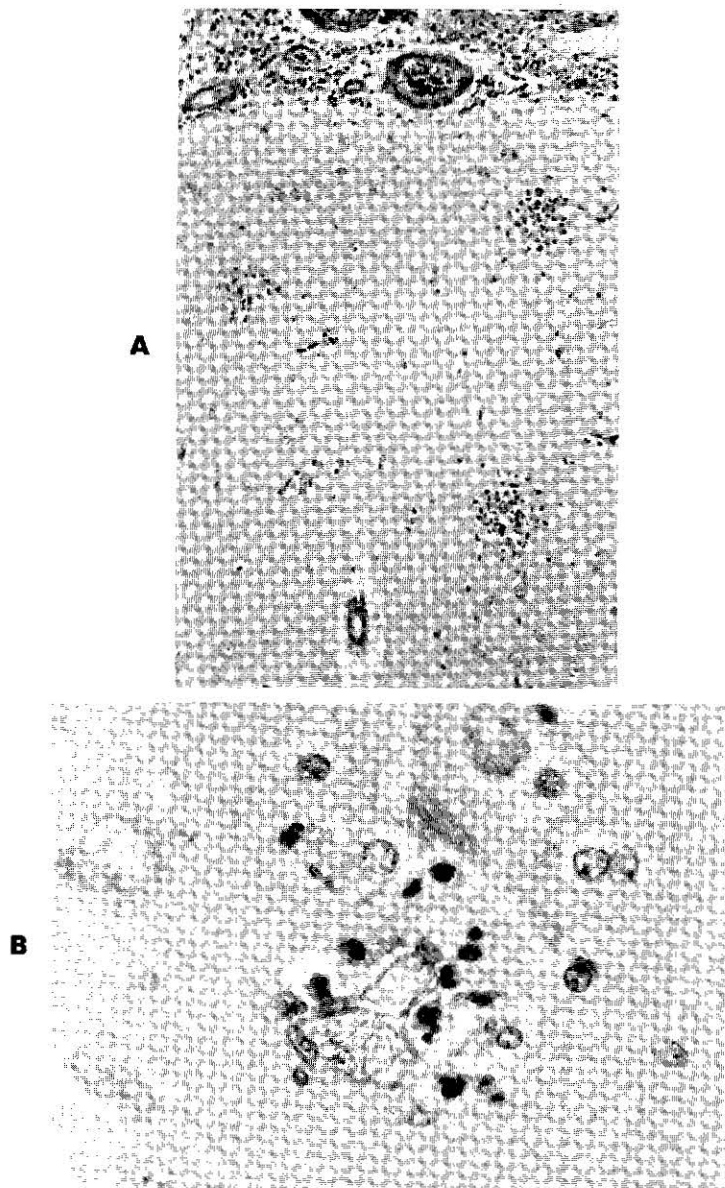


Fig. 5-33. Ethylene glycol poisoning, dog. **A**, Small foci of perivascular inflammation in cerebral cortex. (H&E, $\times 180$.) **B**, Crystal deposition within capillary and neutrophilic response. (H&E, $\times 560$.)

Neuropathological changes are usually lacking; sporadic focal anoxic-ischemic cerebrocortical lesions were observed in one case² and lend some support to the hypothetical role of (excitatory?) neurotransmitters in mediating this neurotoxicosis.

References are on page 337.

ETHYLENE GLYCOL POISONING

Intoxication caused by the ingestion of commercial antifreeze products, which are rich in ethylene glycol, occurs in dogs, cats, and other animals including humans, and a variety of birds.¹ The source is either pure antifreeze solution or after its dilution, such as within water lines or radiator

fluid. Clinical manifestations of poisoning reflect renal insufficiency with vomiting, hypothermia, coma and collapse, and neurological disturbances, most commonly lethargy, ataxia, and seizures.^{2,3} The microscopic hallmarks of this intoxication are abundant pale yellowish oxalate crystals within the renal tubules (mainly proximal) and evidence of nephrosis with attenuated epithelial cells and dilated tubules. Examination of the CNS has been less routine but is worthwhile (Fig. 5-33) as crystals are also present within the lumen or perivascular space of cerebral capillaries.^{2,3}

Only a small fraction of any ethylene glycol absorbed is metabolized, and the end product is oxalate; intermediary compounds, such as glycolic acid, are nephrotoxic. Oxalic

acid may also bind Ca ions, producing a modest hypocalcemia. Neurological signs thus may reflect a metabolic acidosis, uremia, and perhaps hypocalcemic tetany. It is probable that the direct effect of oxalate crystallization within blood vessels of the CNS is of minor clinical importance.

References are on page 337.

HEXACHLOROPHENE POISONING

Hexachlorophene (hexachlorophane), a chlorinated phenol derivative, is a germicide particularly used in soaps and lotions for the control of skin bacteria; it also has fungicidal and anthelmintic properties. In humans, it has been valuable in reducing neonatal staphylococcal infections; however, hexachlorophene is absorbed through the skin and, particularly in low-weight preterm infants, may cause a spongiform myelinopathy.¹ Poisonings have occurred in **dogs** and **cats** following the application of hexachlorophene to skin or ingestion of germicidal soap^{2,4} and probably in **calves** fed from contaminated buckets.⁵ Young animals (neonates) seem to be more susceptible than adults.

Clinical signs of intoxication are reported as diffuse tremors, stiffness or tetanic spasms, seizures, and sometimes death. Experimentally, this clinical picture has been reproduced in several species and can develop within a couple of days of oral administration.⁶ Toxicosis after cutaneous application is usually delayed a few days, although clinical signs within 48 hours have been reported.⁷ At autopsy of natural or experimental cases, there is mild brain swelling from edema. Microscopic examination demonstrates a fairly diffuse spongiform transformation of CNS white matter and mild vacuolation of PNS fibers.⁸ There is mild swelling of astrocytic processes but no microglial response. Ultrastructural findings are of extensive myelin ballooning with splitting of myelin sheaths at the intraperiod line,⁹ common to other intoxicants that incite myelin edema. Hexachlorophene can be detected in blood, brain, liver, and kidney.⁷ In sublethally exposed animals, the tremors resolve; the myelinopathy is largely reversible, although a few vacuoles persist for many weeks.

References are on page 337.

LEVAMISOLE

Levamisole is a broad-spectrum anthelmintic drug¹ that has been widely used in veterinary medicine. Beyond its antiparasitic properties, this drug has considerable effects on the immune system.² These effects are often described as "immunomodulating" and include the restoration of depressed T-cell and phagocytic functions.

Levamisole has been used in the treatment of canine dirofilariasis, a common mosquito-transmitted microfilarial infection. In the course of clinical trials, Vandeveldt and associates³ observed a fascinating effect of this drug on the canine CNS. Although in no sense qualifying as a classical neurotoxicity, the observations are of sufficient interest to warrant brief mention. Orally administered levamisole (5

mg/kg twice daily for varying periods) induced a disseminated accumulation of lymphocytes, plasma cells, and histiocytes around blood vessels and within the meninges of the brain. Both gray and white matter areas were affected. In severe lesions, perivascular cuffs were up to 20 cells thick! Only in the most marked cuffs did these cells infiltrate the adjacent tissue. These changes induced a modest gliosis in perivascular areas, but degenerative changes were minimal. The reaction is reminiscent of granulomatous meningoencephalomyelitis.

By employing differing dosage protocols, it was established that these perivascular aggregates were rapidly induced by the compound, persisted for a few weeks, and then regressed. Severity of the infiltrate, which was quite variable, did not correlate with the duration of levamisole administration.

The basis for this drug-induced, diffuse cerebral inflammation is not known. An anamnestic immune response to latent brain antigens (viral? myelin?) is one speculation. Alternatively, levamisole may activate lymphocytes peripherally, increasing their traffic into the CNS^{4,5} and perhaps initiating perivascular inflammation.

We should also record here the perplexing experience of Sutton and Atwell,⁶ who treated five dogs with levamisole for dirofilariasis; the presenting signs included cough and reduced exercise tolerance. Within a few weeks of their anthelmintic therapy, progressive neurological disease developed. Postmortem neuropathological studies revealed canine distemper encephalitis (2 of 5), granulomatous meningoencephalomyelitis (2 of 5), and an ischemic encephalopathy in the fifth. Unless the apparent cause-and-effect relationship happened purely by chance (many dogs must be treated with this drug without any sequelae), the connection between treatment and subsequent development of neurological disease is perplexing.

References are on page 337.

SELENIUM POISONING AND FOCAL SYMMETRICAL POLIOMYELOMALACIA

An acute, paralytic syndrome has been recognized in young, post-weaning age **pigs** in the United States and Australia.¹⁻³ Pigs of either sex and varying breeds are affected at 2 to 4 months of age. Clinical signs are marked by an abrupt onset of recumbency with flaccid tetraparesis. Some, initially found parietic, are recumbent within 24 to 48 hours. Affected pigs are afebrile, remain bright and alert, and eat and drink if food and water are made accessible to them. Minimally affected animals have improved clinically and returned to an almost normal gait.

At necropsy, there are characteristic lesions in the cervical and lumbar enlargements. Macroscopic areas of softening and cavitation involve the ventral gray columns; lesions are bilateral and symmetrical (Fig. 5-34). When most severe, liquefaction involves the entire ventral horn. Microscopic changes vary, permitting a tentative chronology

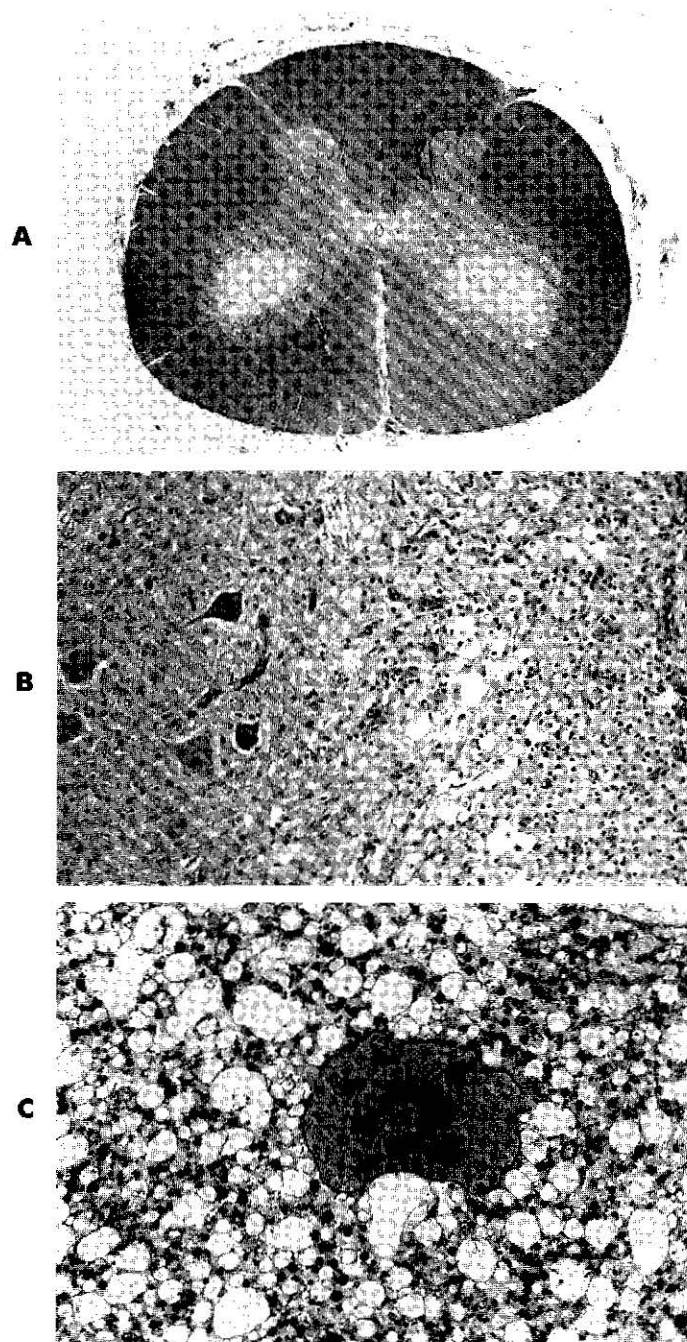


Fig. 5-34. Poliomyelomalacia, pig. **A**, Spinal cord, cervical enlargement. Bilateral degeneration in ventral gray columns. (H&E, $\times 18$.) **B**, Sharp demarcation between viable gray matter and necrotic tissue filled with macrophages. **C**, Electron microscopic appearance of a degenerate motor neuron: condensed, pyknotic nucleus, dilated cisternae in the cytoplasm and granular debris. ($\times 3775$.)

to be constructed. The initial events appear to be a vacuolation of the neuropil, degeneration and necrosis of glial cells, and reactive vascular endothelial swelling. Necrosis and cavitation are accompanied by chromatolytic change in the motor neurons, which hang on until the end. Capillary proliferation is prominent within the necrotic neuropil, and macrophages appear and transform into gitter cells. An infiltrate of a few eosinophils is common. In end-stage lesions, neurons and the neuropil have gone, and capillaries float in a sea of gitter cells within areas of cavitation.⁴ Wallerian degeneration is found in the ventral spinal rootlets. Similar lesions involve gray matter of the brain stem, including the motor nuclei of the fifth and seventh cranial nerves, cuneate and gracile nuclei, reticular formation, and occasionally pontine nuclei, olivary nuclei, caudal colliculus, and cerebellar nuclei.¹

Recent episodes of this syndrome have been associated with toxic levels of dietary selenium, and it has been reproduced by feeding selenium in excess.^{1,2,5} Spontaneously affected pigs have high selenium levels in liver and kidney. A roughness of the hair coat and coronary band inflammation, sometimes leading to sloughing of the hoof, are also seen in affected pigs. Such cutaneous changes have previously been associated with selenium poisoning.

Before an association with selenium was established, O'Sullivan and Blakemore³ had noted a similarity between the lesions in spontaneously affected pigs and those that could be induced by the administration of 6-aminonicotinamide (6-AN), a compound that produces nicotinamide deficiency (nicotinamide is the amide of niacin, a B-complex vitamin). 6-AN is a well-characterized toxin of glial cells of the central^{6,7} and enteric⁸ nervous systems, low doses showing a selective necrosis of reactive astroglia.⁹ Experimental treatment of pigs with 6-AN produced gray matter lesions in the cervical and lumbar enlargements similar to the natural disease.⁶ Ultrastructural studies showed necrosis of oligodendrocytes and vacuolation of astrocytes in gray matter areas. Treated pigs also showed a widespread vacuolation of myelin sheaths, which is not described in the selenium-associated cases. However, both clinically and pathologically, the similarity between the two syndromes is striking. Whether selenium excess induces a nicotinamide-niacin deficiency is unclear, but Wilson and associates¹⁰ have explored this possibility and suggest how selenium excess could antagonize niacin.

Clinically and pathologically similar syndromes have been encountered, on occasion, in other species. In 1952 and 1953, a spinal poliomyelomalacia was responsible for a paralytic disorder of **sheep** in Kenya.¹¹ Disease was usually of sudden onset, involving the thoracic or all four limbs. Bilateral and symmetrical areas of poliomyelomalacia involved the ventral gray columns of the cervical enlargements and, in some sheep, the lumbar enlargements also. In one animal, lesions were found in the medulla and more widespread in the spinal cord. Sometimes the lesions were discontinuous,

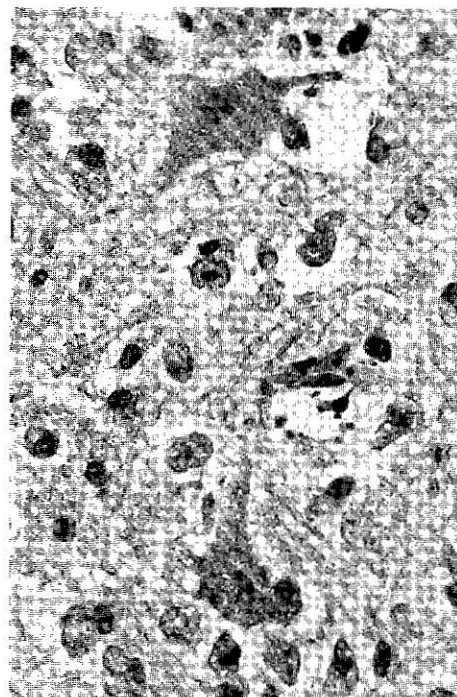


Fig. 5-35. Poliomyelomalacia, goat. Fading necrotic neurons and gitter cells are seen in the ventral horn. (H&E, $\times 560$.)

for example, at C4 and C8, but not at C6. The cause was not established. More recently, multifocal cerebrospinal poliomyelomalacia was reported in sheep in Ghana.¹² Adult sheep were mainly affected, and losses involved up to 72% of the herd. Edema progressing to malacia was found in nuclei of the brain stem and cerebellum and the ventral gray columns of the spinal cord.

In young dairy **goats**, six cases of encephalomyelomalacia have been described by Cordy.¹³ Goats, about 4 months of age, of either sex, and of mixed breeds, showed a sudden onset of tetraparesis. Malacic lesions were found in the brain stem and spinal cord, the latter being more severely affected. Spinal cord lesions (Fig. 5-35) involved the intermediate and ventral columns in the lumbar enlargements, were in both cervical and lumbar enlargements, or were even more widespread. Encephalomalacia was most consistently found in the caudal colliculi.

Focal symmetrical poliomyelomalacia has been described in **Ayrshire calves**.¹⁴ Animals were normal at birth, but within 10 days were weak and unable to stand. Bilateral poliomyelomalacia was found in the lumbar or both the cervical and lumbar enlargements. No abnormalities were found at other levels of the spinal cord or in the brain.

In young **chickens** up to approximately 12 weeks of age, cerebellar encephalomalacia has been associated with nutritional vitamin E deficiency.¹⁵ In **turkey poults**, similar cerebellar lesions, pancreatic necrosis, and lumbosacral poliomyelomalacia, identical to that described previously, have

been observed.¹⁶ Elevating the level of vitamin E in the feed prevented further cases from developing.

A common denominator in these syndromes is necrosis of gray matter in the intumescences, both cervical and lumbar, with some involvement of brain stem nuclei. This pattern suggests a specific syndrome of energy deprivation; at greatest risk would be those segments of the spinal cord with the largest and highest concentration of neuronal cell bodies, namely, the enlargements that house the large, multipolar motor neurons that innervate the limbs. It is of interest that prior to neuronal necrosis, the initial degenerative changes involve neuroglial cells in the gray matter, suggesting that these glia are subservient to the neurons. In the energy-deprivation state of thiamine deficiency, neuronal satellite cells are affected before cortical neurons.

References are on page 337.

TREMORGENIC SYNDROMES

Tremor is a prominent clinical sign in a large number of neurological disorders.¹ The spectrum includes hypomyelinating diseases, inherited metabolic disorders, a variety of intoxications, and idiopathic conditions. Here, we are primarily concerned with a group of toxicological diseases, well recognized in sheep, cattle, and horses² and on rare occasions seen in other species, that are characterized clinically by varying patterns of partial or whole-body tremors. These diseases in grazing livestock are generally ascribed to toxic alkaloids in the pasture grasses or to products of saprophytic fungi. These toxins produce neurological disorders that attain considerable significance in certain geographical areas of the world; their occurrence is typically seasonal. Although most of these tremorgenic syndromes are unassociated with significant or specific neuropathological changes, some of these conditions are briefly described here. These disorders are associated with the ingestion of cultivated grass species, toxic weeds, or contaminated feeds.

Perennial rye grass staggers is a tremorgenic syndrome affecting sheep, cattle, farmed deer, and occasionally horses. It has been recorded most often in Australia, New Zealand, and Britain.³ The disorder occurs in animals grazing pastures predominated by perennial rye grass, *Lolium perenne*, and historically has been related to plant alkaloids such as perloine and halostachine. More recent studies had incriminated mycotoxins such as penitrem A, produced by soil-dwelling *Penicillium* fungi,^{4,5} which can induce a disease like perennial rye grass staggers.⁶ However, these fungi and their toxins could not always be associated with pastures on which perennial rye grass staggers developed. More recent investigations incriminate the commensal fungus *Acremonium loliae*.² This endophyte lives entirely within the plant and is concentrated in the leaf sheath at the base of the plant, although it also grows in the inflorescence and seed. The toxic fungal metabolites are indolic neurotoxins

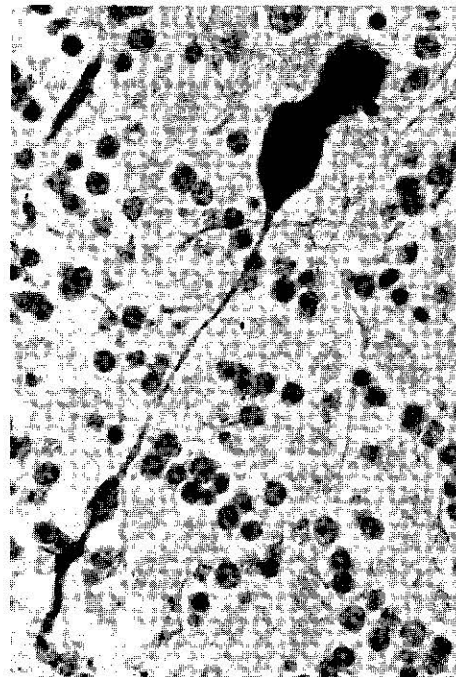


Fig. 5-36. Ryegrass staggers, deer. Swellings along the course of a Purkinje cell axon through the granule cell layer. (Neurofilament immunocytochemistry, $\times 715$.)

called lolitrems,^{2,7} which if administered to mice produce a tremor syndrome.

Animals (most commonly sheep) are affected in late summer and autumn while grazing short stubble (3 to 5 cm). The prevalence of the disorder varies considerably from year to year. In a bad season, 30% morbidity in sheep flocks and 10% mortalities are known; in flocks of thousands of animals, losses can be considerable. In New Zealand, it is estimated that several million livestock may be involved in some summers.⁸ Signs of disorder are usually precipitated by disturbing or driving the flock, although fine head tremors may be seen at rest.⁸ Affected sheep move with stiff limbs, producing an ataxic, bounding gait. Falling triggers seizures, and heavily pregnant ewes may be unable to rise. At times of stress, such as during a drought, losses can be heavy. Most affected animals regain their feet some minutes after collapsing, and removal from toxic pastures effects a full recovery in 1 to 3 weeks.

Specific pathological changes are lacking. In chronic cases, swelling of the proximal segments of cerebellar Purkinje cell axons (torpedoes) are found,⁹ remarkably so in deer (Fig. 5-36), and occasional swollen axons are seen elsewhere throughout the neuraxis. The acute and transitory neurological deficits, in the absence of significant morphological changes, raises the likelihood that perennial rye grass staggers is a functional neurological derangement, perhaps of neurotransmission.⁸

Consumption of moldy cream cheese¹⁰ or moldy hamburger bun¹¹ has produced a tremorgenic syndrome in dogs. The clinical manifestation of this toxicosis is severe, generalized muscle tremors, ataxia, and intermittent seizures. Anesthesia to control seizure activity results in a virtual cure in 12 hours. The food was contaminated with the mold *Penicillium crustosum*, which produces the tremorgenic toxin penitrem A. Intoxication of cattle resulting in trembling and deaths has been associated with *Penicillium* and *Aspergillus* molds contaminating feedstuffs.¹² A neurological disorder was observed in Scottish cattle and lambs given a feed supplement contaminated with *Aspergillus clavatus*.¹³ Frothing at the mouth, stiffness, knuckling, and ataxic gait were noted. Some of the affected animals became recumbent. Postmortem examination of affected lambs revealed neuronal chromatolysis in the red and vestibular nuclei (Fig. 5-37), spinal cord ventral horns, and spinal ganglia. The spinal cord had a Wallerian degeneration in all funiculi, and a primary axonopathic effect was proposed. A neurological disorder affecting cattle and less frequently sheep in South Africa is associated with the consumption of maize on which the fungus *Diplodia maydis* is growing.¹⁴ The clinical signs are not marked by tremor but by ataxia and paresis or paralysis. Affected animals recover if the source of moldy feed is removed.

Annual ryegrass staggers is a disorder of complex pathogenesis that may affect ruminants (mainly sheep), horses, and pigs; it is recognized in Australia and South Africa. Morbidity and mortality rates are variable, but mortality may reach 100%,¹⁵ resulting in economically devastating losses. The disorder occurs in animals grazing annual ryegrass (*L. rigidum*), in which the seedheads are infested with a nematode *Anguina agrostis*. The galled seeds contain a bacterium, *Corynebacterium rathayi*, carried into the ryegrass by the nematode larvae. In some parasitic galls, the bacteria proliferate, the nematodes die, and toxic bacterial galls result.¹⁵ Corynetoxins, produced by *C. rathayi*, are responsible for the tremorgenic syndrome, which occurs when animals are disturbed or stressed.

Clinical signs may be seen from a few days up to 3 months after exposure to toxic pastures, which is usually in late spring to summer. Affected animals have a staggering gait, collapse, and 2- to 3-minute seizures with spastic limbs.^{16,17} Pregnant ewes may abort, and animals unable to regain their feet die.

Pathological findings are of fatty, friable livers and evidence of disrupted vascular integrity, resulting in edema and congestion of lungs, lymph nodes, and CNS. Microscopically, there is consistently an effusion of plasma in the cerebellar leptomeninges and focal areas of degeneration in the neuropil. Experimental intoxication demonstrated increased transendothelial vesicular transport (transcytosis).¹⁸

Corynetoxins are glycolipids that inhibit glycosylation, resulting in depletion of essential basement membrane glycoproteins. The lethal dose of the corynetoxins for sheep

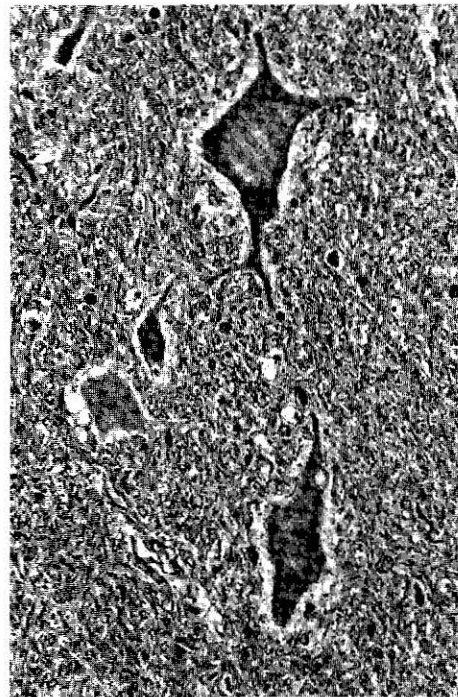


Fig. 5-37. *Aspergillus* mycotoxicosis, cow. Swollen, chromatolytic neurons in brain stem. (H&E, $\times 350$.)

has been established,¹⁹ and the effects of experimental intoxication in sheep¹⁸ and rats²⁰ have been studied. The tunicamycin antibiotics are closely related to the corynetoxins, and the CNS effects of tunicamycin have been examined.²¹ In brief, these experimental studies suggest a primary vascular (capillary) injury and astrocyte swelling, with areas of localized ischemia.

A disorder clinically and pathologically similar to annual ryegrass staggers resulted in the death of more than 3000 cattle in New South Wales, Australia, in 1990 and 1991. Cattle were grazing pastures that had previously flooded, which generated the term **flood plain staggers**. Affected cattle had episodes of seizures with opisthotonus, salivation, and limb paddling. The pasture grasses included *Agrostis* sp (blown grass or blow-away grass), and the seed heads contain a toxin-producing *Clavibacter* bacterium.²²

Paspalum staggers is a tremorgenic syndrome that affects cattle and, to a lesser degree, sheep and horses in New Zealand, Australia, the United States, South Africa, and elsewhere.²³ The disorder is a mycotoxicosis, caused by ingestion of paspalum grasses harboring the fungus *Claviceps paspali*.^{24,25} The fungal mass (sclerotium or ergot body) that replaces the seed contains tremorgens related to those produced by *Penicillium cyclopium*.² Affected animals show hyperesthesia, tremors, and ataxia and, if driven, may collapse temporarily.^{23,26} Morbidity rates may be up to 50% of a herd of cattle, but mortality is usually below 10%. No specific lesions are recognized. *Claviceps purpurea* can in-

vade cereal grains and pasture grasses, producing a sclerotomy containing many toxic alkaloids. Acutely poisoned horses and sheep show ataxia, paraplegia, and seizures; cattle more commonly develop gangrene of the extremities due to arteriolar constriction.²⁵ Phalaris grasses are valuable pasture species, but toxicity has been associated with *Phalaris aquatica* (formerly *P. tuberosa*), *P. minor*, and *P. angusta* in Australia, New Zealand, and, more recently, the United States and Argentina.^{27,28} Sheep and cattle are affected. Two distinct forms of intoxication are recognized: A peracute syndrome may follow recent access to pasture and results in collapse from cardiac arrhythmias, presumably due to tryptamine alkaloids that potentiate serotonin and catecholamines; chronic poisoning—**phalaris staggers**—follows some weeks after grazing phalaris-dominant pastures. This form can be prevented in sheep by supplemental cobalt, which presumably enhances the degradation of plants by rumen microbes. Affected sheep are normal at rest but, if handled, are hyperexcitable and have muscle tremors, including involuntary head nodding. If driven, there is some hypermetria and truncal ataxia; pelvic limbs are stiff and are advanced together or dragged. The animals stagger and finally collapse; sheep unable to rise have periods of paddling tetanic seizures with salivation and spontaneous nystagmus. If undisturbed, some regain their feet and slowly recover, but repeated episodes can be fatal. At necropsy of animals with the neurological syndrome, the kidneys and brain stem have a greenish gray discoloration.^{29,30} Microscopically, neurons of the brain stem and spinal cord (ventral horn) contain a brown granular pigment (Fig. 5-38), identified ultrastructurally within mitochondria in one report³¹ and lysosomes²⁹ in another. In one study, pigment-bearing macrophages were observed within CSF.²⁹ A mild Wallerian degeneration affects the pyramidal tracts extending into the spinal cord. The stored indole-like neuronal pigment and its relationship, if any, to the clinical syndrome are unclear. This appears to be a further tremorgenic syndrome caused by a functional rather than a structural aberration. The serotonergic activity of some *Phalaris* alkaloids has been proposed as the basis for the chronic disorder.³² Affected sheep may show signs for as long as 5 months after removal from the pasture.²⁹ Intoxicated cattle have muscle tremors, are ataxic, show stiff pelvic limb movements, and have a peculiar impairment of tongue movement,²⁷ producing dysphagia, which results in slow starvation.

Tremorgenic syndromes have been seen sporadically in cattle grazing common or coastal Bermuda grass or fed Bermuda grass hay.^{2,33} A variety of poisonous plants, including white snakeroot (*Eupatorium rugosum*), Jimmy fern (*Notholaena sinuata*), and mountain laurel (*Sophora secundiflora*) incite tremorgenic or tremorgenic-like syndromes in grazing stock. Specific changes in the neuraxis are not described.^{2,34}

A syndrome encountered sporadically in the dog, prob-

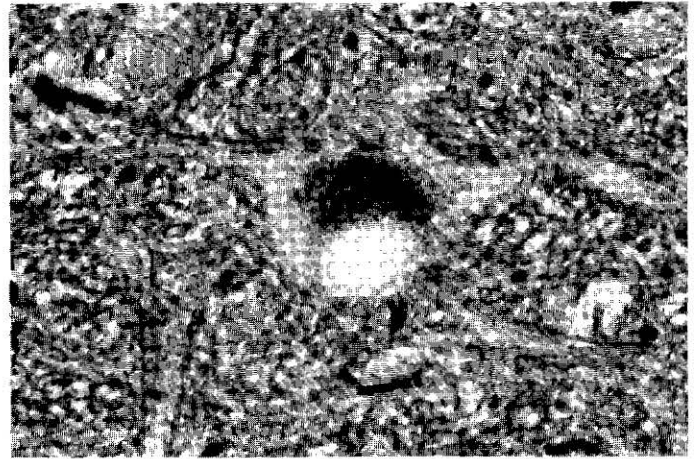


Fig. 5-38. Chronic phalaris poisoning, cow. Cytoplasmic pigment granules in a neuron, red nucleus. Vacuolation of neurons in this nucleus is normal in cattle. (H&E, $\times 560$.)

ably not an intoxication, is worthy of brief mention. This condition of acquired whole-body tremors is recognized in **white-coated dogs** of a variety of breeds.³⁵ This disorder is seen in the Maltese Terrier in the United States³⁶ and in Australia (Farrow, personal communication 1985) and in the West Highland White and Beagle breeds. The clinical signs of constant, whole-body tremors suggests diffuse CNS disease, probably of white matter. Hypomyelination in a variety of species produces a similar clinical disorder. This canine syndrome is often corticosteroid responsive. Few cases recover spontaneously. Sometimes a mild lymphocytic pleocytosis is observed on CSF analysis,^{1,36} and in the few dogs we have examined postmortem, CNS myelin was normal, but there was evidence of a diffuse, very mild non-suppurative encephalomyelitis consisting of scattered, narrow, lymphocytic perivascular cuffs. An acquired immunological disorder affecting neurotransmitter synthesis has been hypothesized.³⁵

References are on page 338.

EQUINE NIGROPALLIDAL ENCEPHALOMALACIA

A clinically and pathologically unique neurological disorder occurs in horses following prolonged ingestion of yellow star thistle (*Centaurea solstitialis*) or Russian knapweed (*C. repens*). This disorder was first described by Cordy in California¹ and subsequently in other areas of the United States in association with one of these plants;² it has also been reported from Argentina and Australia.³

These weeds offer horses attractive forage in summer months when other unimproved pasture has wilted, whereas cases do not occur on weed-free, irrigated fields. After ingestion for approximately a month (*C. repens*) or longer (*C. solstitialis*), horses precipitously develop difficulties in prehending food and, to a lesser degree, in drinking. The

mouth is partially open, frequently with the tongue protruded and the muzzle and lips fasciculate while the horse is trying to eat. Any food acquired is retained in the mouth, sometimes for hours. In contrast, swallowing appears to be unaffected. Affected horses are inactive and somnolent with a fixed facial expression; some wander aimlessly with the head lowered to the ground. Death results from starvation and dehydration because of inability to prehend. Affected horses are typically younger stock (2 years of age or less).³ Ruminants may graze the same fields without ill effect.

At necropsy, there are characteristic discrete yellowish areas of malacia in the globus pallidus and substantia nigra. Over half of the cases have bilateral lesions in both nuclei, but bilateral lesions in only the pallidum or the nigra, unilateral lesions, and lesions in a few other brain stem nuclei occur in a minority of cases.^{3,4} Microscopically the areas of necrosis are sharply demarcated from viable tissue with virtually no transitional zone. Neurons, glial cells, blood vessels, and any fibers passing through the nuclei undergo coagulation necrosis and are removed by macrophages.

Experimental reproduction of the syndrome has been attained with both plants, of which *C. repens* appears to be the more toxic. In contrast, feeding these plants to small laboratory animals, monkeys, and dogs is unrewarding. The toxic principle is unknown, and the basis for its selective targeting of these two nuclei remains to be explained. Poisoning seems to occur when, after consumption for some weeks, a threshold is reached, precipitating acute necrotizing changes. Dopamine deficiency may underlie some of the clinical deficits in this syndrome,³ inviting analogies with Parkinsonism.

References are on page 338.

SOLANUM POISONING IN CATTLE

An acquired syndrome of cerebellar ataxia in cattle has been recorded in South Africa, the United States, and Brazil. In each area, there is an association with plants of the genus *Solanum*, and the syndrome has been experimentally reproduced by feeding the plant to calves. The incriminated plants are *S. kwebense*¹, *S. dimidiatum*² and *S. fastigiatum*.³ Clinically and pathologically the syndromes are virtually identical. Affected cattle, which range from 6 months to 10 years of age, often appear normal until disturbed or excited, which precipitates an episode of a seizure-like activity or severe disorientation with loss of balance. The neck is rigidly extended, thoracic limbs stiffen, and nystagmus may develop. The animals stagger sideways or backwards and may fall to the ground. In regaining their posture, they are base-wide and crouched and show a hypermetric ataxic gait, eventually returning to an almost normal posture and appearance.

Morbidity in a herd is variable, but may be 20% or higher. Death is uncommon, usually resulting from accidents (drowning) to which affected cattle are predisposed. Some have to be euthanized because of severe injuries incurred

by repeated falls. When affected cattle show signs, they rarely recover, and if severely affected will become wasted. Poisoning is said to occur where pastures are overgrazed, perhaps compelling cattle to consume more of the weed than is normal.

At necropsy, the brain is normal or shows atrophy of the cerebellum, involving all lobules. The ratio of cerebellar to whole-brain weight may be required to establish this in equivocal cases (it should be approximately 10% to 12% of brain weight). Histological examination reveals a process of progressive cytoplasmic vacuolation of Purkinje cells of the cerebellar cortex (Fig. 5-39, A), proceeding to lysis and disappearance. This loss of cell bodies is attended by a proliferation of astrocytic glia, which extend marginally into the molecular layer. Swollen Purkinje cell axons (spheroids) are observed in the granule cell layer, white matter of the cerebellar folia, and medulla. Wallerian degeneration accompanies the progressive Purkinje cell loss. Occasional small cuffs of lymphocytes and macrophages may also be seen. Neuronal vacuolation also affects the nuclei of the cerebellar medulla and occurs sporadically elsewhere in the brain stem. Ultrastructural examination of affected Purkinje cells shows the accumulation of membranous cytoplasmic bodies (Fig. 5-39, B) and lamellar bodies; the latter are common in Purkinje cells in a variety of pathological conditions and can be found, in lower numbers, in normal Purkinje cell bodies and axons.⁴

This syndrome in cattle, associated with the progressive accumulation of cytosome bodies in Purkinje neurons, is reminiscent of the lysosomal storage diseases, and the membranous cytoplasmic bodies observed are a hallmark of the gangliosidoses. Furthermore, some of these storage conditions can be induced by plants. However, as this effect is largely limited to cerebellar Purkinje cells, and extensive necrosis of affected populations is unusual in the lysosomal storage diseases, this condition may represent an intoxication with a plant substrate that these neurons in particular cannot readily metabolize by lysosomal (or perhaps other) pathways. In other studies, the administration of various compounds with lysosomal enzyme-inhibiting properties induced the formation of cytoplasmic inclusions in neurons and neuroglia.⁵ Sometimes Purkinje cells and other large neurons were preferentially affected.⁶ This plant-induced condition would seem to offer a convenient tool with which to study clinical and pathological aspects of cerebellar cortical disease.

In Australia, a myelopathy of sheep (popularly known as humpyback) results from the ingestion of *S. esuriiale*. This condition is discussed with other miscellaneous toxicoses.

References are on page 338.

CYCAD POISONING

Poisoning of cattle following the consumption of cycad (or zamia) palms (family Zamiaceae, genera *Cycas*, *Ma-*

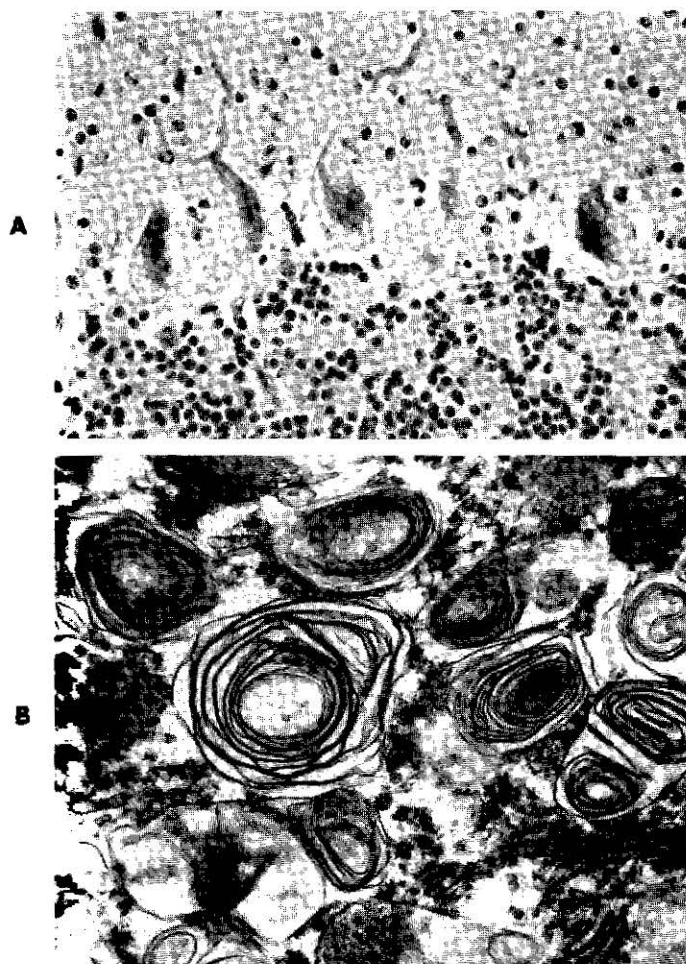


Fig. 5-39. *Solanum fastigiatum* intoxication, cow. A, Vacuolar change in cerebellar Purkinje cells. (H&E, $\times 350$.) B, Electron microscopy reveals membranous storage material. ($\times 32,900$.)

crozamia, and *Bowenia*) occurs in the northern parts of Australia, Papua New Guinea, Puerto Rico, and the Dominican Republic.^{1,2} Since the 1960s there has been interest in the theory that the high incidence of amyotrophic lateral sclerosis-Parkinsonism-dementia complex on Guam is a consequence of the use of cycad seeds as food and medicine. Recent studies in primates^{3,4} have reactivated this hypothesis, although this work has been challenged on several grounds.⁵

In an historical article on cycad poisoning in Australia, Hall⁶ describes reports of poisoning in Captain Cook's men and their pigs during his discovery of Australia in 1770. Mason and Whiting² commented that cattlemen have been aware for a century of the association between cycad ingestion and a crippling disease in their stock. Hall⁷ associated these three genera with either of two syndromes, one an hepatic lipidosis and fibrosis, and the other paraparesis and ataxia.

The clinical and neuropathological changes, in a limited number of natural and experimental cases in cattle, were

reported by Hall and McGavin.¹ Affected cattle had a stumbling, ataxic pelvic limb gait with the hind quarters swaying from side to side. Progressively, the animals weaken, sink in the pelvic limbs, and walk with the hoof knuckled over or collapse. Hall⁷ associated this neurological syndrome with consumption of the leaves. Experimental feeding of cycad leaves to two steers reproduced the syndrome,¹ one receiving *B. serrulata* and the other *M. lucida*. The pathological effects may vary from one cycad palm to another, apart from the quantity consumed. Calves and cattle of all ages seem to be susceptible, and chronic cases remain permanently disabled.² Intoxication can occur when alternative green feed is available and seems to reflect individual animal preference for the plant.⁸

At autopsy, there is a bilateral and symmetrical myelopathy, well delineated by the Marchi technique for degenerate myelin. Affected fibers are in the fasciculus gracilis, mostly in the cranial thoracic and cervical spinal cord. In the lateral funiculus, the dorsal spinocerebellar tracts are affected, with less prominent involvement of ventral spinocerebellar fascicles. Affected fibers extend in a rim below the pia into the ventral funiculus to the ventral median sulcus. Hooper and associates⁹ observed axonal spheroids with a similar distribution. Degenerate fibers in the ascending pathways can be traced to the gracile nucleus and caudal cerebellar peduncles in the brain stem.

References are on page 339.

MISCELLANEOUS POISONS

A large number of toxic substances sporadically incite neurological disease in animals. Some involve poisons that may be important in humans but rarely affect animals, such as carbon monoxide. Others are causes of animal disease on an infrequent basis, for example, with idiosyncratic reactions to drugs, or are important only in certain regions of the world, as occurs with several poisonous plants. This discussion is devoted to this group of miscellaneous neurotoxicoses.

In South Africa, a myelopathy of 2- to 4-month-old lambs is thought to be associated with ingestion of the plant *Chrysocoma tenuifolia*.¹ Affected lambs have a stumbling, crawling gait, sometimes advancing while dragging the pelvic limbs behind them. Many die or must be killed; they have a diffuse myelopathy with chromatolysis and vacuolation of all spinal cord neuronal populations, particularly the ventral gray column. The lateral and ventral funiculi are spongy, particularly in the areas of the dorsal spinocerebellar tract and other peripheral tracts below the pia in the lateral and ventral funiculi. These lesions resemble the changes observed in swayback, but liver copper levels are normal.

In an area of New South Wales, Australia, a slowly progressive ataxic disorder of adult sheep has been recognized since 1937.² This "staggers" syndrome is most common in sheep older than 4 years of age; it progresses over several months from early pelvic limb paresis and basewide

stance, through a phase of dropping of the pelvis with stifle and hocks flexed, to recumbency. A mild to moderate Wallerian degeneration is found throughout the spinal cord funiculi, maximally in lumbar segments. The disorder is believed to result from ingestion of the plant *Tribulus terrestris*, which grows abundantly at times when other vegetation is lacking. Evidence of decreased levels of dopamine and its metabolite 3,4-dihydroxyphenylacetic acid have been demonstrated in the basal nuclei of affected sheep,³ but the relationship of this observation to the myelopathy and the clinical disease is unclear. Within the family Zygophyllaceae, plants of the genera *Peganum*, *Kallstroemia*, and *Tribulus* have been associated with locomotor disorders in sheep and cattle.⁴

Humpy back is a colloquialism for a myelopathy of adult sheep in Queensland, Australia. The syndrome occurs in the summer months, some weeks after rainfall. Signs in sheep increase with age; mild lesions have been observed in clinically normal animals.⁵ The morbidity is usually 5% or less, but is occasionally higher.

When affected sheep are forced to walk for at least a mile, they fall behind the flock with a stilted, stiff pelvic limb gait. At rest, they stand with the head lowered and back arched, a posture from which the name is derived. A period of rest affords some degree of recovery.

At necropsy, there is extensive Wallerian degeneration in all funiculi of the entire spinal cord. Degeneration ascends into the caudal cerebellar peduncles. Myopathic changes, probably a secondary development, are found in some cases. This syndrome has been recognized for more than 40 years, and a plant poisoning has been considered the most probable cause. O'Sullivan⁵ and McMeniman⁶ provide evidence that *Solanum esuriale* is the offending plant.

A further plant-induced toxicosis in Australia is a syndrome of blindness and neurological disease in goats and sheep following ingestion of the perennial shrubs *Stypandra imbricata* and *S. glauca*.^{7,8} Also recognized and studied in the 1930s, this condition is characterized by blindness and an acute illness in which some animals show CNS signs, including pelvic limb paresis and ataxia, collapse, and death, sometimes from misadventure. Some animals survive and largely recover but are permanently blind, with dilated, unresponsive pupils. In goats there can be simply depression and separation of affected animals from the herd, with preservation of vision and slow resolution over a few weeks.

Neuropathological findings depend upon the stage of the disease at the time of examination. Acutely poisoned animals have a diffuse white matter spongiosis (myelin edema) that consistently involves the optic nerves and optic tracts; changes in the corpus callosum, internal capsule, cerebellar peduncles, spinal cord, and peripheral nerves are more variable. In more chronically affected animals, severe degeneration of the optic nerves ensues, particularly of the intracanalicular segment. There is a severe loss of axons and their myelin sheaths, gitter cell formation, astrogliosis, and

a thickening of the lamina cribrosa. The optic nerves become progressively shrunken and atrophic, and Wallerian degeneration extends along the optic tracts to the lateral geniculate nuclei. Myelin edema and optic neuropathy are accompanied by retinal degeneration with pigment epithelial hypertrophy and hyperplasia and degeneration of photoreceptor and outer nuclear layers.

Optic nerve and retinal injury are both believed to be primary changes, occurring independently of each other. Huxtable and associates⁹ have reproduced the intoxication in rats and studied the evolution of the myelin spongiosis (splitting of myelin sheaths at the intraperiod line) and the retinopathy. Optic nerve degeneration may result from edematous swelling and consequent ischemia of that portion within the bony canal and/or a selective direct axonopathy. The toxic principle is a binaphthalene tetrol that has been designated stypandrol. In South Africa, blindness and paresis or paralysis have been observed in sheep and occasionally cattle following consumption of the plant *Helichrysum argyrosphaerum*.¹⁰ Treatment of sheep with **rafoxanide** (a fasciolicidal drug) has produced blindness.¹¹ In both of these conditions, there is a retinopathy and CNS white matter spongiosis, as in *Stypandra* poisoning.

In horses, cystitis and ataxia have been associated with the ingestion of *Sorghum* plants.^{12,13} The clinical presentation is of pelvic limb ataxia with a weaving, swaying gait. This is usually accompanied by urinary incontinence, which reflects the acute to chronic cystitis. The CNS lesion is a diffuse Wallerian degeneration in the lateral and ventral funiculi of the spinal cord, extending into the brain stem. A similar disorder has been described in cattle.¹⁴

The genus *Astragalus* contains a few hundred species of plants, many of which make valuable livestock feed. Some members of the genus are toxic:

1. The so-called locoweeds, which contain inhibitors of lysosomal α -mannosidase (see the section about mannosidosis)
2. The selenium-accumulating *Astragalus* species
3. The nitro-bearing *Astragalus* species, which may produce a chronic ataxia and paresis in grazing animals (mostly cattle), typified by a staggering gait and knuckling at the fetlocks;^{15,16} respiratory difficulties are common also, and at necropsy, Wallerian degeneration can be found in the spinal cord and peripheral nerves.

The antiparasitic drug **ivermectin** has been found to be toxic in Collie dogs and sometimes other dog breeds.¹⁷ Following oral administration salivation and vomiting, confusion, ataxia, tremors, and coma may be seen.¹⁸ With supportive therapy, complete recovery is usual. Ivermectin is known to stimulate the release of γ -aminobutyric acid; intoxicated Collies have elevated levels of dopamine and serotonin metabolites in their CSF,¹⁹ reflecting increased activity of dopaminergic and serotonergic neurons. Elevation of the level of these monoamine neurotransmitter metabo-

lites may be associated with the neurological complications. Toxicosis is not the result of increased absorption or diminished clearance from plasma.²⁰

Treatment of dogs with **metronidazole** may induce a transitory CNS toxicosis. This drug is used to treat giardiasis, trichomoniasis, and anaerobic infections in humans and dogs, and in both species neurological signs have been seen. Approximately 7 to 12 days after treatment, severe ataxia to the point of recumbency, opisthotonus, positional nystagmus, muscle spasms, and occasionally seizures have been seen in dogs.^{21,22} The CSF protein levels were mildly elevated in two of three dogs. Neuropathological studies of intoxicated dogs revealed axonal swellings in vestibulocerebellar pathways and brain stem leukomalacia.²¹ Most affected dogs, except for the most severely disabled, recover within a week or two of drug withdrawal.

Furazolidone is commonly incorporated into animal rations to control colibacillosis. Prolonged feeding to calves can produce a granulocytopenic and thrombocytopenic disorder. Neurological disturbances have also been encountered in calves and pigs with ataxia, muscle tremors, hyperexcitability, and seizures.^{23,24}

Carbon monoxide is a sporadic cause of human fatalities where solid heating fuels burn incompletely in the face of restricted air supply. Doubtless such deaths in cabins and other confined areas have at times involved domestic animals also,²⁵ as well as farm animals in heated barns. Death by deliberate inhalation of the carbon monoxide in automobile exhaust fumes is a common means of suicide.

The neural lesions of human carbon monoxide poisoning are a curious mixture of cerebral hemispheric white matter degeneration and necrosis with focal coagulation or ischemia in the globus pallidus, substantia nigra, and hippocampus.^{26,27} Primates and cats have been subjected to experimental carbon monoxide poisoning as models for the human disease, and lesions of similar distribution are seen. Changes in the cerebral white matter begin with axonal necrosis, conglutination of axonal organelles, and secondary effects on myelin sheaths, with ballooning and the formation of empty myelin figures.²⁷

Carbon monoxide binds avidly to hemoglobin to produce carboxyhemoglobin, which lacks oxygen-transporting capacity. Carbon monoxide probably binds other enzyme systems also, thus producing both anemic and histotoxic anoxia. There are detrimental effects on cardiovascular function, and the case has been made that the cerebral white matter lesions correlate well, in intoxicated cats, with the fall in blood pressure.²⁷ Why the cerebral cortex is largely spared is a tantalizing question that remains to be satisfactorily answered. A remarkably similar distribution of necrotizing cerebral lesions was recorded in a cat with a leukoencephalopathy resulting from **cyanide** poisoning;²⁸ the same question is pertinent here also. However, Hartley²⁹ found cerebrocortical malacia in two dogs with cyanide poisoning.

Bromethalin-based rodenticides will produce acute neurological disease with muscle tremors, hyperexcitability, and seizures if consumed by dogs and other animals in excess of tolerated doses.³⁰⁻³² The CNS lesions are a diffuse white matter spongiosis with myelin splitting and vacuolation.³³ Lesser quantities produce a more delayed pelvic limb paresis and ataxia. The anthelmintic combination of **toluene** and **dichlorophen** may cause ataxia, depression, disorientation, hyperesthesia, tremor, and other abnormalities in dogs and cats.³⁴

References are on page 339.

EDEMA DISEASE

Edema disease of swine is a syndrome that has been recognized since 1938, when Shanks¹ described this condition in Ireland. It most commonly is an acute, highly lethal disorder of previously healthy and thriving pigs, occurring at or soon after weaning. The clinical signs, sometimes preceded by a day or two of mild diarrhea,² are mostly referable to neurological dysfunction; the disease is so named for the prominent visceral edema found at postmortem examination, characteristically affecting the forehead, stomach wall, and mesenteries. As Shanks noted, a common association is a sudden change in the system of feeding.

Edema disease usually affects pigs between 4 to 12 weeks of age and may occur in a few animals in one litter or in epizootics. In one outbreak spanning 5 months described by Yoshikawa and colleagues,³ 200 of 700 pigs had various expressions of the associated neurological disease—the mind boggles! Early in an outbreak, some pigs may be found dead; within 2 or 3 days, affected littermates develop an ataxic, staggering gait, head tilt or torticollis, aimless wandering, impaired vision, circling, terminal seizures, coma, and death. Acutely affected pigs reveal the classical necropsy findings of edema of the subcutis of the forehead and eyelids, submucosal edema of the stomach, mesenteric edema, and edema of lymph nodes, gall bladder, and elsewhere. In contrast, pigs with a subacute to chronic neurological course may not show these characteristic gross changes. Gross neuropathological changes are grayish foci of encephalomalacia, extending from the caudate nucleus to the medulla but most consistently in the mesencephalon and myelencephalon. These foci are bilateral and symmetrical in most but not all cases. Microscopically, these quite sharply demarcated lesions display an early pallor and microvacuolation of the tissue (Fig. 5-40, A), ischemic necrosis of neurons and glial cells, and, in a few days, a histiocytic influx. Such necrotic foci liquefy and, if large, cavitate, to be filled with gitter cells and scattered capillaries. Fibrous astrocytes proliferate at the margins among scattered spheroids. The lesions have been described as demyelinating,⁴ but that term should be restricted to changes characterized by selective loss of myelin.

Vascular changes in the neuraxis are present in all animals but more so in those with less fulminating disease. This is

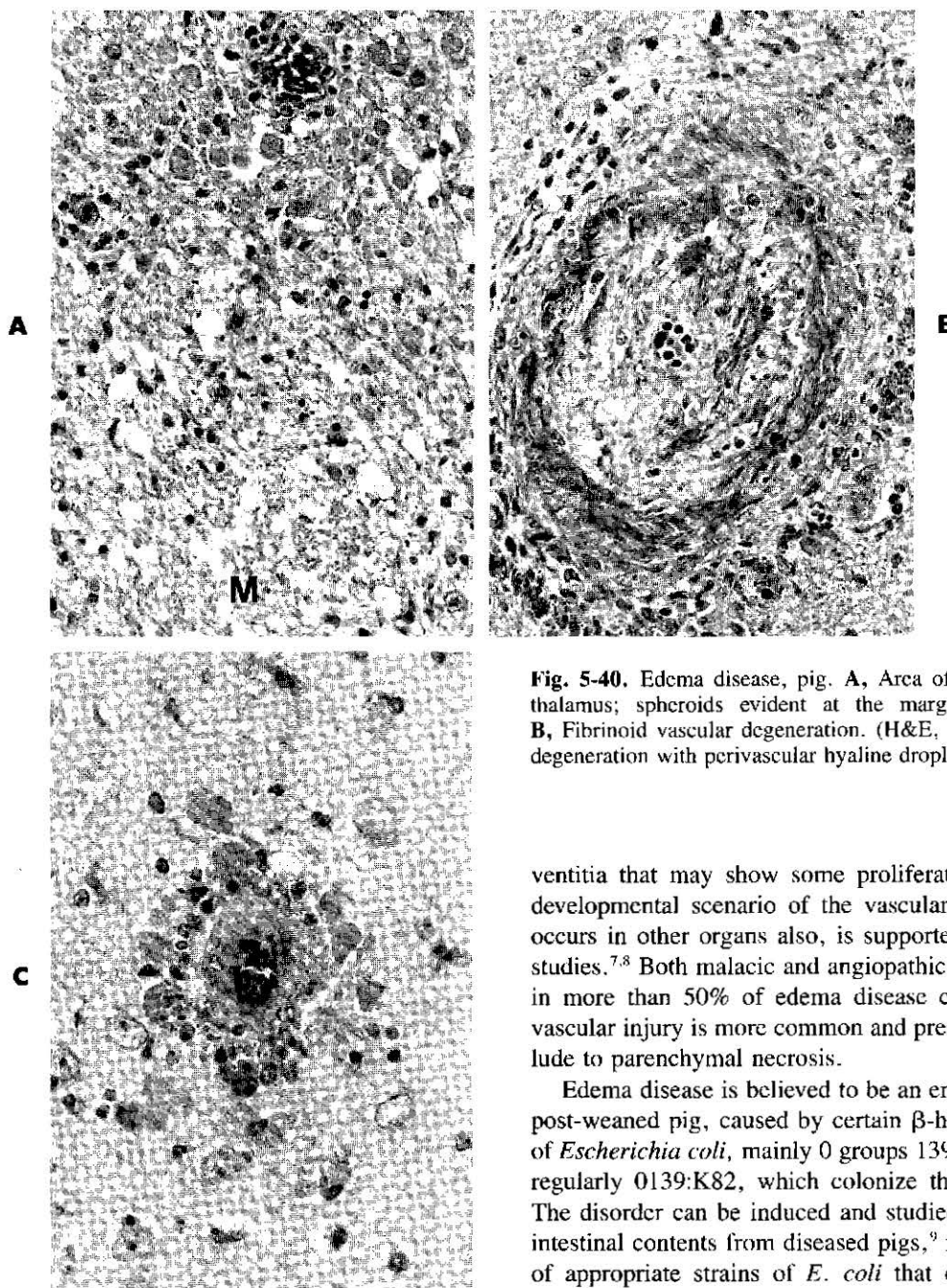


Fig. 5-40. Edema disease, pig. **A**, Area of malacia (*M*) in the thalamus; spheroids evident at the margin. (H&E, $\times 350$.) **B**, Fibrinoid vascular degeneration. (H&E, $\times 360$.) **C**, Vascular degeneration with perivascular hyaline droplets. (H&E, $\times 560$.)

a cerebrospinal angiopathy⁵ affecting small arteries and arterioles in the neuroparenchyma and leptomeninges.⁶ Vascular changes (Fig. 5-40, *B*, *C*) appear to begin with edema and some swelling of the tunica media and of the intimal endothelial cells; this progresses to fibrinoid necrosis and karyorrhexis of medial smooth muscle cells. Characteristically, droplets of hyaline, eosinophilic material are found surrounding such blood vessels, apparently deposited in the neuropil at the glia limitans. Early hyaline changes in vessels are readily identified by the PAS stain. There is then a progressive, modest mononuclear cell infiltrate of the ad-

ventitia that may show some proliferative changes. This developmental scenario of the vascular pathology, which occurs in other organs also, is supported by experimental studies.^{7,8} Both malacic and angiopathic changes are found in more than 50% of edema disease cases. Of the two, vascular injury is more common and presumably is the prelude to parenchymal necrosis.

Edema disease is believed to be an enterotoxemia of the post-weaned pig, caused by certain β -hemolytic serotypes of *Escherichia coli*, mainly O groups 139 and 141 and most regularly O139:K82, which colonize the small intestine.² The disorder can be induced and studied using extracts of intestinal contents from diseased pigs,⁹ freeze-thaw lysates of appropriate strains of *E. coli* that contain the edema disease principle,¹⁰ and a *Shigella dysenteriae*-like toxin, the Shiga-like toxin II variant, which may be the crucial factor.^{11,12} Hemolysin and cell-free autolysates, when administered to pigs, best recapitulate the characteristic pathological changes, but endotoxin may play a role in producing acute deaths in outbreaks of this disease.⁹ Interestingly, the edema disease principle also induces hypertension in swine,¹³ a further possible contributing factor to vascular injury.

In summary, a pathogenesis involving a circulating angiotoxin inducing vascular injury (perhaps with primary endothelial damage¹⁴), vasogenic edema, hypoperfusion, and ischemia is envisioned. Analogies can be made with focal

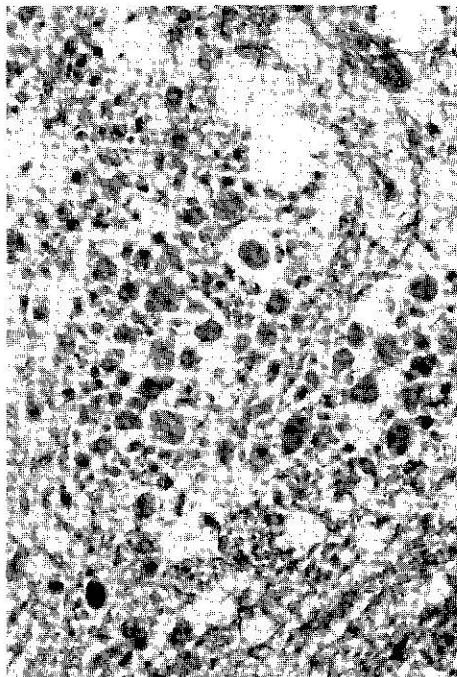


Fig. 5-41. Focal symmetrical encephalomalacia, sheep. Area of malacia with spheroids in cerebellar peduncle. (H&E, $\times 350$.)

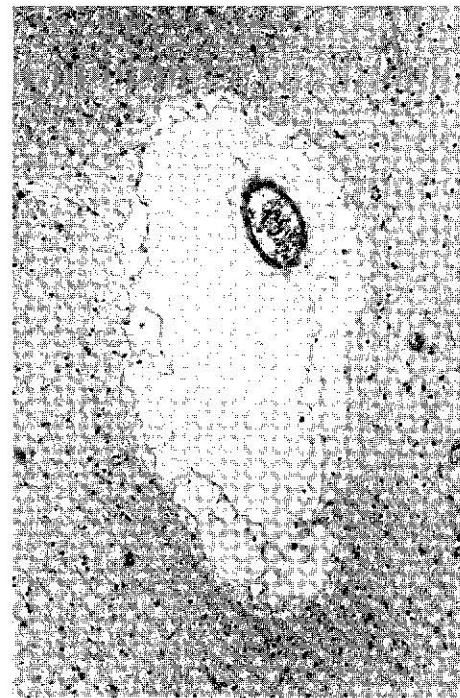


Fig. 5-42. Enterotoxemia, sheep. Perivascular lake of edema fluid, external capsule. (H&E, $\times 140$.)

symmetrical encephalomalacia of sheep and equine leukoencephalomalacia.

References are on page 339.

FOCAL SYMMETRICAL ENCEPHALOMALACIA

Focal symmetrical encephalomalacia of lambs (FSE) was first reported from New Zealand by Hartley¹ and then soon after in Great Britain.² Hartley studied a neurological disorder of young lambs, mostly 2 to 8 weeks of age, which ran a course of a week or so; older lambs, up to 6 months, and occasionally older sheep succumb.³ Affected lambs were markedly depressed, ataxic, wandered aimlessly, and, in a few cases, appeared blind. Some were prostrate and had seizures; a few died peracutely. At postmortem examination, transverse sections of the brain revealed focal, bilateral, and symmetrical malacic lesions in the internal capsule and adjacent basal nuclei, thalamus, mesencephalon, and cerebellar peduncles. Lesions varied from pinkish, hemorrhagic zones to soft, yellowish gray foci. In those lambs that died without premonitory signs, three of four had gross postmortem findings of enterotoxemia in the thorax and abdomen. Some also had distinct, bilateral hemorrhagic lesions (of similar distribution) in the brain.

Microscopic examination of the brain revealed acute, sharply demarcated areas of parenchymal necrosis and hemorrhage. Neurons, glial cells, axons and myelin were necrotic, and such foci quickly liquefied. Early cellular infiltrates were polymorphonuclear, but these were soon re-

placed by macrophages that progressively became distended with necrotic debris. Capillaries, often with swollen endothelia, were prominent, a common feature of the response to CNS necrosis. Phagocytosis and removal of tissue debris proceeded, leaving a loose cystic cavity populated with gitter cells and capillaries. In the adjacent, less-injured tissue, axonal spheroids (Fig. 5-41) were found with a few perivascular mononuclear cells.

Lambs affected with FSE often came from properties where enterotoxemia (due to *Clostridium perfringens* type D) had caused mortalities. Hartley proposed that FSE was also a manifestation of *Cl. perfringens* type D intoxication, perhaps induced by lower doses than those that precipitate the acute syndrome we know as enterotoxemia or "pulpy kidney" disease. It seems that there is a spectrum of disease; in classical enterotoxemia, young lambs die peracutely, intestinal enterotoxin can usually be demonstrated, and any brain lesions are most frequently microscopic.⁴ These changes, in the distribution of FSE lesions, are of protein-rich perivascular edema (Fig. 5-42), hemorrhages, and malacic foci. In FSE, the clinical course is subacute, the signs indicate diffuse brain injury, intestinal toxin is less readily demonstrated, and macroscopic evidence of multifocal encephalomalacia is found. The two forms are probably not distinct, but ends of a continuum.

Experimental reproduction of the acute and subacute effects of *Cl. perfringens* type D toxin in lambs and mice⁵ were consistent with the natural disease. An early effect of

the toxin, demonstrable within 3 to 6 hours of administration, was increased vascular permeability in the brain.⁶ Ultrastructural studies in lambs⁷ and mice⁸ revealed early swelling and degeneration of astrocyte end feet, with increased cytoplasmic density of vascular endothelia. Leakage of horseradish peroxidase through blood vessels was demonstrable within 50 minutes of toxin administration. Preferential binding of activated epsilon toxin to brain tissues, compared to other organs, has been shown.⁹ It thus seems that in peracute enterotoxemia, circulating toxin acts primarily on the vasculature in visceral tissues. In the syndrome of FSE, perhaps occurring in partially immune lambs or with lower levels of toxin absorbed, the effect is mainly on CNS vessels—a vasogenic edema. Increased transendothelial vesicular transport may initiate the swelling of astrocyte foot processes. Pathogenetically, FSE would seem to share features with the neurological expression of edema disease of swine.

As a general rule, CNS edema is most severe in white matter, where astrocytes take up the excess fluid and swell until they are lysed. In FSE, the tissue necrosis may also have an ischemic component, resulting from glial swelling, which impinges upon and collapses small-caliber vessels.

FSE, primarily a disease of young sheep, has been observed in calves,^{10,11} although only rarely. These reports in cattle are presumptive and based upon the similarity of the brain lesions to those seen in sheep with FSE. Buxton and colleagues¹¹ described three cases associated with peracute CNS disease and death. Bilaterally symmetrical foci of malacia were in the internal capsule and adjacent basal nuclei, thalamus, midbrain, and cerebellar peduncles. Munday and associates¹⁰ reported FSE in a 6-week-old recumbent, apparently blind, opisthotonic calf. In another report,¹² macroscopically evident symmetrical malacic foci were found in the internal capsule and cerebellar peduncles of two young calves. Microscopic involvement extended to the basal nuclei and thalamus. Interestingly, in this paper, the authors describe a case of enterotoxemia (*Cl. perfringens* type D) in a 4-month-old calf, with plasma lakes around venules in the internal capsule and cerebellar peduncles, mirroring the CNS changes present in lambs with enterotoxemia.

Although enterotoxemia is well recognized in goats, a subacute neurological form appears not to occur in this species.

References are on page 340.

EQUINE LEUKOENCEPHALOMALACIA

An acute neurological disorder of horses and other equidae, associated with the ingestion of moldy feed, has been recognized since the last century. The syndrome occurs worldwide, with a regional distribution reflecting climatic conditions that favor fungal growth on feed. In the United States, it is seen mostly in the midwestern and southern states. Furthermore, there is a seasonal pattern, with most cases occurring from late fall to early spring. Clinical signs

begin abruptly; affected horses are afebrile and may be jaundiced. In some, there is an initial period of somnolence and depression with impaired food prehension and mastication. This soon gives way to ataxia, aimless walking, blindness, head pressing, and, terminally, hyperexcitability and seizures. Affected horses succumb in a few hours to 3 to 4 days. Those that recover may be "dummies."

At necropsy, there are unilateral or bilateral, gray to brown areas of malacia and cavitation in the centrum semiovale and corona radiata of the cerebral hemispheres (Fig. 5-43).¹ Microscopically, these areas of liquefactive necrosis are filled with glial cells that merge into zones of intact but pallid tissue, with congested blood vessels and proteinaceous, perivascular edema that dissects into the tissue. A few vessels have perivascular cuffs of lymphocytes and eosinophils. Degenerating axons and myelin abound. The lesions are largely confined to cerebral white matter but may extend focally into the cortical mantle. Lesions occur also in the brain stem, cerebellum, and spinal cord.² The liver may be shrunken and nodular with histological changes ranging from periportal necrosis to portal fibrosis, bile duct proliferation, hepatocellular lipidosis, and multinucleated hepatocytes.³

Leukoencephalomalacia of equidae is a mycotoxicosis caused by consumption of a corn-based feed contaminated with the fungus *Fusarium moniliforme*.⁴ The syndrome has been reproduced with this mold,³ and of its many mycotoxins, the metabolite fumonisin B1 has been implicated.⁵ Both the liver and the CNS are target tissues, and this is reflected in spontaneous and experimental cases in which both hepatic disease and leukoencephalomalacia may be found concurrently. Hepatic injury is rarely the predominant finding, and the neurological signs are presumed to be due to the encephalomalacia. Experimentally, the severity of hepatic and neural lesions can be manipulated with toxin



Fig. 5-43. Leukoencephalomalacia, horse. Transverse section of cerebrum and brain stem. Severe degeneration of white matter of dorsal corona radiata.

dose; low levels are thought to favor the development of CNS damage,⁵ although natural cases of leukoencephalomalacia have occurred where large quantities of contaminated corn have been consumed within a short period.⁹

The pathogenesis of this disorder is uncertain, but the inference is that circulating fungal toxins show a selective tropism for blood vessels of cerebral white matter. Vascular injury, resulting in perivascular edema, swelling, and sub-

sequent necrosis of glial cells, may initiate lesion development. In this respect, analogies can be drawn with focal symmetrical encephalomalacia of sheep.

A case of leukoencephalomalacia in a White-tailed deer¹⁰ and a neurological disorder affecting horses and rabbits, associated with an *F. tricinctum* mycotoxicosis, have been described.¹¹

References are on page 340.

Nutritional diseases

VITAMIN A DEFICIENCY

Deficiencies of vitamin A (retinol) leading to the development of neurological disorders have been reported in several domestic and non-domestic animal species;¹ perhaps cattle and swine are most often affected. Cattle are at risk if raised in arid areas,² when grazing drought-stricken pasture, or if maintained under feedlot conditions and fed concentrates³ without access to green forage. Often it is suspected (usually retrospectively) that storage of feeds in hot, humid, sunny conditions has depleted β -carotene levels in the feed. Episodes in pigs occur when the diet consists largely of grain (wheat or barley) and lacks vitamin supplementation.

The clinical manifestations of hypovitaminosis A in calves include a diminished appetite, poor growth, diarrhea, ataxia, seizures, and blindness. Falling serum vitamin A levels approximate the progression of clinical signs.² Sometimes congenitally affected calves are born from deficient dams; they are weak, ataxic, and blind, and some may be stillborn.⁴ In adult cattle, ataxia, seizures, and blindness are commonly seen.⁴

With respect to the pathogenesis of the neurological disease, vitamin A deficiency affects bone growth, particularly remodeling, and also CSF absorption. In affected adult cattle, bone growth has ceased, and so derangements of CSF flow are proffered as the basis for the neurological disorder; in calves, it seems that both factors are operative. An early manifestation of vitamin A deficiency in cattle is papilledema,⁵ a consequence of elevated CSF pressure and possibly the optic nerve compression that occurs in the optic canal. The development of blindness, with widely dilated and unresponsive pupils, follows. Some animals can be demonstrated to be night blind.² Ophthalmoscopic examinations, as well as revealing the optic disk swelling, may show retinal detachment and subretinal hemorrhages.⁶ Papilledema is reversible in the early stages.⁷

At necropsy, the diagnostic findings are compression of neural tissue within the cranium (Fig. 5-44). Herniation of the cerebellar vermis is frequently observed. Congenitally affected calves may have domed calvaria with thickened occipital, basisphenoid, and presphenoid bones. The optic

canal is mildly to severely narrowed in a dorsoventral plane, and the intraosseous portion of the optic nerve is compromised (Fig. 5-45). Its degeneration is evident from the yellow-brown discoloration of the nerve, but sometimes only a thick fibrous cord remains. There is collagenous thickening of the entire intracranial dura mater, particularly at the entrance to the optic canal and at the optic chiasm.⁸ Microscopically, involvement of the lamina cribrosa is seen also. Fibrous tissue replaces the degenerate and gliotic optic nerve. Congenitally affected calves may be hydrocephalic.

Blindness in vitamin A-deficient calves (and other animals) is mediated in several ways. Night blindness (nyctalopia) results from rhodopsin deficiency and is reversible by administering vitamin A. Prolonged deficiency results in progressive narrowing of the optic canal due to the continued addition of new bone to its dorsal surfaces and the failure of bone resorption from the lateral and ventral aspects.⁹ Optic nerve injury results from direct compression by the narrowed canals and is compounded by ischemia; antero-

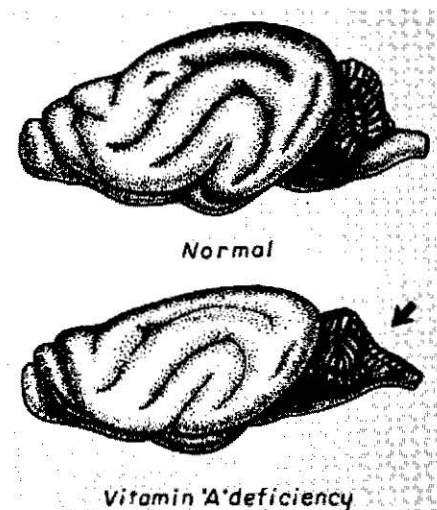


Fig. 5-44. Vitamin A deficiency, mink. In the affected animal, the cerebrum is flattened and the cerebellum is herniated (arrow).



Fig. 5-45. Vitamin A deficiency, calf. Intraosseous portion of the optic nerve. **A**, Normal. **B**, Vitamin A-deficient calf: Notice severe degeneration of the optic nerve and smaller optic canal compared to **A**.

grade Wallerian-type degeneration occurs in the optic chiasm and optic tracts. Additionally, a retrograde degeneration occurs in the proximal optic nerve and associated retinal ganglion cells. Early elevated CSF pressure produces papilledema, but there is also diffuse photoreceptor degeneration⁹ and pigment epithelium hypertrophy. Congenitally affected calves may show occasional retinal folds,⁴ and in newborn depleted piglets there may be severe ocular dysplasia and anomalies in other organ systems.¹⁰

Calves with adequate hepatic stores of vitamin A take 6 months or so to become depleted, depending upon their stage of growth and the duration and severity of the deficiency. Steers seem to be more susceptible to the effects of vitamin A deficiency than are heifers.⁹ In summary, clinical disease in cattle progresses from elevated CSF pressure with papilledema, through reduced growth and nyctalopia to seizures and, in calves, optic nerve injury. Seizures and ataxia seem to reflect increased intracranial pressure² and are responsive to replenishment of depleted vitamin A. In deficient calves,¹¹ fibrosis and deposits of amorphous material in the stroma of arachnoid granulations may impede CSF drainage.

In pigs as in cattle, hypovitaminosis A diminishes reproductive performance. Neurological signs, in young animals, may begin with a swaying, ataxic, pelvic limb gait progressing to tetraplegia.^{1,12} Seizures and blindness are also seen. At necropsy, the brain is flattened and herniated, the optic nerves are compressed, and Wallerian degeneration is found in the spinal cord.

References are on page 340.

VITAMIN E DEFICIENCY

A spectrum of neurological disorders has been associated with chronic vitamin E deficiency in humans.¹ Spinal cord degeneration with prominent axonal dystrophy, pigmentary retinopathy, and myopathy are some of the syndromes that are observed. Vitamin E depletion may result from alimentary malabsorption, chronic cholestasis, or abetalipoproteinemia. In adults, years of depletion may be necessary for clinical signs to develop, whereas children may become symptomatic earlier. Rats² and primates³ maintained on vitamin E-deficient diets develop degenerative changes in the dorsal columns and sensory nerves similar to those of humans. The physiological role of vitamin E is one of protecting membrane phospholipids from oxidant injury by free radicals. Axonal dystrophy of the gracile and cuneate nuclei is seen in vitamin E deficiency and also in normal mature and aged animals. This has lead Kay and associates⁴ to propose oxidation as a possible mechanism of cellular aging.

In animals, the range of disorders associated with hypovitaminosis E is remarkably broad.⁵ Skeletal and cardiac myopathies are well recognized, and retinopathy has been described in the dog.⁶ Neurological disorders are best documented in young **chickens**, in which nutritional deficiency produces a cerebellar encephalomalacia.^{7,8} Cerebellar deficits are clinically evident, and grossly the organ is edematous, swollen, and sometimes hemorrhagic. Microscopically, necrosis may be found involving the molecular layer, Purkinje and granule cell neurons, and folial white matter. Similar cerebellar lesions are observed in vitamin E-defi-

cient **turkey** poults; these birds may also have spinal poliomyelomalacia.^{9,10} In the domestic animals with which we are primarily concerned, vitamin E deficiency has most strongly been incriminated in **equine degenerative myeloencephalopathy** and is discussed further with that disease.

The distal axonopathy of experimental vitamin E deficiency in rats is associated with delayed anterograde and retrograde axonal transport.¹¹ This may be a sequel to oxidant injury to mitochondria, which would interfere with energy-dependent processes within the axon.

References are on page 340.

COPPER DEFICIENCY: SWAYBACK AND ENZOOTIC ATAXIA

A neurological disorder of newborn and young lambs, first described in the 1930s but known well before that period, has been recognized worldwide where sheep are raised. This ovine encephalomyelopathy is known as **swayback** or **enzootic ataxia**; some authors use these terms as synonyms, whereas others reserve swayback for the congenital form and designate the delayed-onset pattern as enzootic ataxia, a policy we employ here in the interest of clarity. Investigations ultimately associated this disease in sheep with a state of copper deficiency and showed that the treatment of pregnant ewes with copper successfully prevents its development. Clinically and pathologically similar disorders are recognized in young goats and pigs, perhaps calves, and adult deer. An association with copper deficiency in these other species is also suspected, but the relationship is less clear.

Copper deficiency may be primary, affecting the soil, the plants that grow in it, and the animals that graze on these plants. In secondary deficiencies, other substances interfere with the animals' ability to utilize copper: such include molybdenum, zinc, cadmium, and inorganic sulfates. Even the type of food ingested affects copper absorption: It is poorly absorbed from fresh herbage but well from cereals.¹

Copper is an integral element in several enzyme systems such as ceruloplasmin and lysyl oxidase,² and copper deficiency affects several organ systems. Swayback and enzootic ataxia in lambs may be accompanied by unthriftiness, anemia, and fleece abnormalities (poor crimp) in their dams, all manifestations of copper deficiency. Copper deficiency myelopathy in pigs may be attended by abnormalities of elastin formation in the aorta and pulmonary arteries, points of potential rupture, and skeletal abnormalities with fractures.³

The clinical expression of fetal copper deficiency in **sheep** is as follows: Congenitally affected lambs (**swayback**), which can have severe cerebral lesions, are dull and may be blind and deaf, often lying prostrate with flaccid limbs. Occasional cases are stillborn. If they can stand, they commonly fall when attempting to move, and affected lambs

commonly succumb within the first few days of life. Approximately half have grossly evident cerebral changes. When the calvaria is removed, the cerebral hemispheres are fluctuant and in severe cases have collapsed. The lesions affect the cerebral white matter (centrum semiovale and corona radiata) bilaterally and symmetrically, and vary from small focal to extensive lesions (Fig. 5-46, A). There is a progressive gelatinous transformation of the white substance, ending in cavitation that qualifies as porencephaly or hydranencephaly. The lateral ventricles undergo a secondary dilation. Microscopically, a transition from intact myelinated tissue, to a rarefied, edematous change of the tissue, to cavitation can often be found. Evidence of myelin degradation by histiocytes is sparse, and Cancilla and Barlow have commented that these cerebral lesions begin in utero before significant myelination has occurred. Ultrastructurally, neuritic and fibrillary astroglial processes span the greatly enlarged extracellular spaces.⁴ Laminar neuronal necrosis, sometimes with calcified neurons, can be found in the cerebral cortex overlying areas of white matter rarefaction or cavitation (Fig. 5-46, B). Most published studies have described the changes in the newborn lamb, the end point of an insult that acts on the developing fetal brain. Our understanding of the histogenesis of this cerebral lesion leaves much to be desired.

In **enzootic ataxia**, lambs are clinically unaffected at birth but develop a swaying pelvic limb ataxia soon thereafter, up to approximately 6 months of age. Mildly affected lambs show only gait deficits when driven, but in others the pelvic limb paresis and ataxia are blatant. The deficits are progressive. In some, forelimbs are also slowly affected, and the mortality rate is high. The signs may reflect lower motor neuron involvement with flaccid paresis and hypotonia, hyporeflexia, and atrophy of muscles. In enzootic ataxia, CNS lesions are microscopic and affect neuronal populations and white matter in the brain stem and spinal cord (Fig. 5-47). Neuronal changes are of total chromatolysis with perikaryal swelling and eosinophilia, dissolution of Nissl flakes, eccentricity and pyknosis of the nucleus, and, in some, necrosis. Neurons of the red and vestibular nuclei, the reticular system of the medulla, spinal cord ventral motor neurons, and nucleus thoracicus are most consistently, although not exclusively, affected. Ultrastructurally, these chromatolytic neurons are depelted of ribosomes and contain aggregates of enlarged mitochondria and abundant fascicles of neurofilaments.⁵ Accompanying these neuronal changes is a diffuse, bilateral, and symmetrical degeneration of white matter affecting the caudal brain stem and all segments of the spinal cord. The distribution is tract related, mainly involving the dorsal spinocerebellar fibers and their extension into the caudal cerebellar peduncles and spinal cord tracts adjacent to the ventromedial fissure. The tissue is pale staining, depleted of axons and myelin, and variably astroglitic. Ballooned myelin sheaths (digestion chambers), which contain occasional macrophages, are best

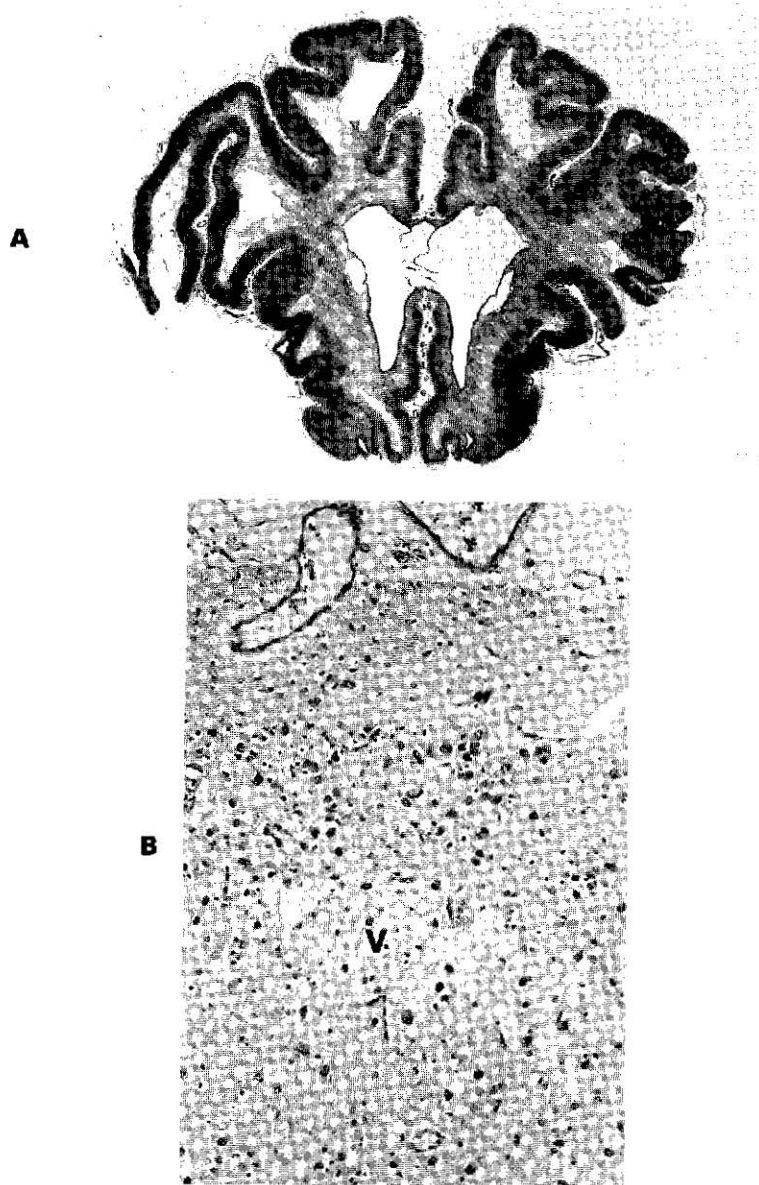


Fig. 5-46. Congenital swayback, lamb. **A**, Degeneration and cyst formation within cerebral white matter. Lateral ventricle is dilated. (H&E, $\times 3$.) **B**, An area of the cerebral cortex from **A** to show vacuolar degeneration (v) of the neuropil and neuron loss within middle laminae. (H&E, $\times 140$.)

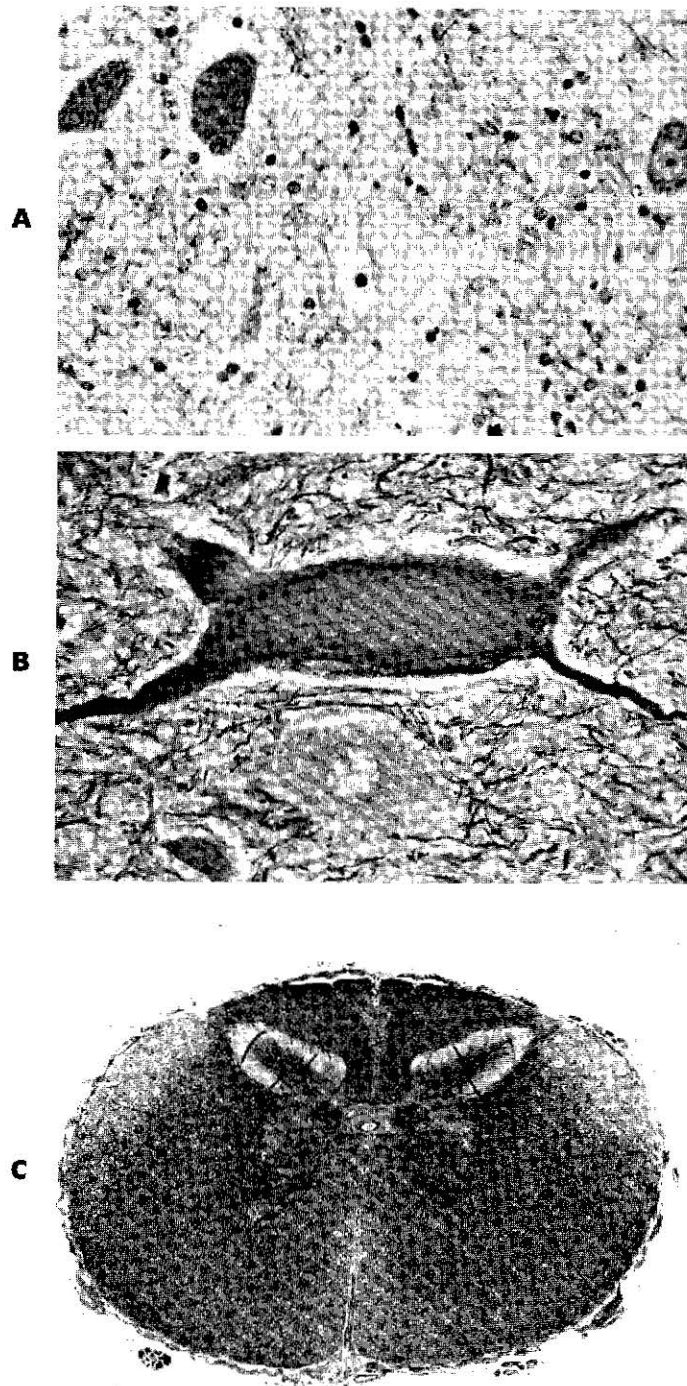


Fig. 5-47. Delayed swayback, goat. **A**, Swollen, chromatolyzed neuron, spinal cord. (Luxol fast blue, cresyl echt violet, $\times 350$.) **B**, Chromatolyzed and neurofilament-filled neuron in spinal cord. (Holmes silver, $\times 560$.) **C**, Cervical spinal cord: pronounced degeneration in the dorsal part of the lateral funiculus. Mild degeneration adjacent to dorsal and ventral fissures.

appreciated in longitudinal sections of the tissue. Electron microscopic findings are of primary axonal degeneration with secondary loss of myelin.⁶

The distribution of neuraxial lesions in lambs with clinical abnormalities at birth (swayback) and in those with a delayed onset (enzootic ataxia) overlap. Consistent to both are the neuronal chromatolytic changes and fiber degeneration in the brain stem and spinal cord.^{7,8} In swayback, approximately half have grossly visible cerebral lesions; the others have only microscopic changes. In enzootic ataxia, the lesions are only microscopic. Liver copper levels in both may be as low as 10 ppm.

A unique form of copper deficiency in lambs in England was one of severe cerebral edema.^{9,10} Affected lambs, in the first 6 weeks of life, showed severe ataxia and whole-body tremors that rapidly progressed to recumbency and death. Postmortem findings were of severe cerebral edema with herniation of the cerebellar vermis through the foramen magnum. Curiously, cerebral swelling was sometimes largely unilateral. The examination of brains of lambs with cerebral edema under ultraviolet light revealed autofluorescence,¹¹ an observation usually associated with cerebral necrosis. The authors commented that this disease lies somewhere between cerebrocortical necrosis and swayback.

In swayback and enzootic ataxia, the lesions in the spinal cord are often described as demyelinating, which implies selective myelin loss in the face of axonal preservation. However, ultrastructural examinations have revealed changes consistent with a primary axonopathic effect.⁶ The bilateral distribution of these lesions in fiber tracts, rather than a random disposition of plaques, favors a primary axonal basis. It is likely that copper deficiency impedes the ability of large multipolar neurons to sustain their axons, which begin to degenerate toward their distal extremities, a unifying hypothesis proposed by Cavanaugh that seems to cover several neuraxial insults. Neuronal populations prone to chromatolysis are depleted of the mitochondrial respiratory chain enzyme cytochrome oxidase, but other copper-containing enzymes, such as superoxide dismutase, are probably affected also. Biochemical aberrations precede morphological changes, the latter in large neurons appearing earliest in distal axons farthest from the perikaryon. Hence distal axonopathy may be evident before chromatolysis. In swayback, the cerebral white matter lesions evolve after normal neuronal migration has occurred, are evident by day 99 of gestation,⁸ and perhaps reflect a failure to maintain adequate axonal elongation in the growing brain.⁶ The mechanism whereby copper deficiency is responsible for these diverse changes in the developing fetal nervous system⁸ is very poorly understood. The pattern of disease that develops (swayback, sometimes with gross cerebral cavitation, or enzootic ataxia with microscopic changes in neurons and spinal cord white matter) may be influenced by the timing and severity of the deficiency, by whether the deficiency is primary or secondary, and perhaps by other

factors. For example, during cell differentiation (and particularly in CNS populations), oxygen utilization generates increased levels of superoxide anion.¹² Protection against superoxide radicals requires the enzyme superoxide dismutase, of which the fetal brain utilizes the copper- and zinc-containing form. Copper deficiency may predispose the growing, differentiating nervous system to oxygen radical injury.

Copper deficiency in **goat kids** is manifest as enzootic ataxia and only rarely¹³ as the congenital form with cerebral lesions. In one study of 23 cases, progressive paresis and ataxia were evident between 5 and 28 weeks of age.¹⁴ There may be spastic or flaccid paraparesis or tetraparesis, which can mimic the caprine arthritis encephalitis syndrome (CAES).¹⁵ Although CAES lesions are most often in white matter, it can affect gray matter in the intumescence, which would give flaccid signs. Unlike CAES, spinal fluid in caprine enzootic ataxia may show no abnormalities.¹⁶ Hypermetria and head tremor may be also evident, reflecting the patchy cerebellar degeneration or atrophy that is seen in approximately half of the goats with enzootic ataxia, but is rare in affected lambs. Microscopic examination of the cerebellum demonstrates Purkinje cells that are chromatolytic and hyalinized, and some are ectopic.^{14,17} Radial astroglia proliferate in response to the Purkinje cell loss, the granule cell layer is depleted, and the molecular layer is thinned. Spinal cord funicular lesions and neuronal chromatolytic changes are as in lambs. Wallerian degeneration in the ventral spinal roots and peripheral nerves is more common than in lambs. Central nervous system lesions have been found in goats with no neurological signs.¹⁷ Liver copper levels of affected kids are often low, but not uniformly so,¹⁶ and clinically normal herdmates with similarly low or even lower levels can be found.¹⁷ In affected kids, tissue copper levels are not as low as in affected lambs.

Pelvic limb paresis associated with low liver copper levels has been recorded sporadically in **pigs**^{18,19} up to 4 to 5 months of age. Ataxia progresses to paraplegia within a week or two. Lesions are microscopic and involve the white matter of the brain stem and spinal cord as described previously. Changes in neurons are not recognized. Liver copper levels are often around 5 to 10 ppm,^{18,20} but clinically normal piglets may have similar levels.³ In some piglets, abnormalities of elastic fibers in the aorta and pulmonary artery are demonstrable, and occasional sudden deaths result from vascular rupture.³

Very rarely it has been suggested that copper deficiency in young **calves** is associated with neurological disorder and CNS lesions, but the evidence is far from convincing.²¹

In various breeds of **mature deer**, a syndrome that has been designated enzootic ataxia has been observed in England, continental Europe, and New Zealand.²² As deer are now commercially farmed, this disorder may be of some importance. At first there is stiffness of movement, unsteadiness of the hindquarters, and a tendency for excessive re-

cumbency. This is progressive, ultimately leading to death after a very chronic course. The lesions are as for enzootic ataxia of sheep.²³ Liver copper levels are generally below 20 ppm, but such levels are not confined to animals with ataxia.²⁴ Sporadic episodes of diffuse Wallerian degeneration of the spinal cord in llamas, wildebeest, and camels²⁵ may on occasion be a manifestation of copper deficiency.

In humans, **Menkes' disease** is a sex-linked, inherited disease²⁶ resulting from disordered copper homeostasis. The human condition remarkably recapitulates many features of dietary copper deficiency in animals as discussed here, including softening and cavitation of cerebral white matter, laminar cerebrocortical necrosis, chromatolytic neuronal degeneration in the reticular formation, cerebellar atrophy, and tract degeneration in the spinal cord. Other tissues are affected as in animals, including the skin and hair, and the human disorder is also known as kinky (or steely) hair syndrome. The male, **brindled, mottled mouse** mutant shares clinical, biochemical, and pathological features with Menkes' patients²⁷ and has been studied as a model of the human disease.²⁸

References are on page 341.

THIAMINE DEFICIENCY AND POLIOENCEPHALOMALACIA

A progressive encephalopathy has been associated with thiamine (vitamin B₁) deficiency in a surprisingly wide range of domestic animals, both ruminants and carnivores, and some non-domesticated animals. This is also a human disease (Wernicke's encephalopathy), classically associated with chronic alcoholism. The circumstances under which a state of thiamine deficiency transpires varies between the large and small animals prone to develop this disorder. Neuropathological alterations are also varied in their distribution and somewhat in their character, being most pronounced in the cerebral cortices in cattle, sheep, and goats and in periventricular nuclei of the brain stem in carnivores. The disorder in dogs and cats is uniformly accepted as a thiamine deficiency encephalopathy, whereas the ruminant disease is often said to be thiamine responsive, the implication being that the pathogenesis in these animals may involve thiamine indirectly. Furthermore, accumulating evidence incriminates other nutritional factors, apart from vitamin B₁, in the ruminant disease.

In **cattle, sheep, and goats**, this syndrome was recognized well before the role of dietary factors was appreciated and was named **polioencephalomalacia**¹ (PEM) or **cerebrocortical necrosis**² (CCN). Despite the inherent nonspecificity of these two terms, they have become the common designation for this disorder in the United States (PEM) and England (CCN). It is well recognized, however, that similar neuropathological lesions can result from other causes such as lead poisoning, water deprivation, or hypoxia. In ruminants, PEM may develop in animals housed in feedlots or at pasture. Cases, frequently involving several animals,

are most common in the first year or so of life, whereas sporadic episodes affect older animals. Signs of the disorder are typically abrupt in onset and often begin with depression, muscular tremors, and separation from the group. Isolation may reflect blindness, which is of cortical origin. In some animals, a brief bout of diarrhea precedes the development of neurological signs,^{3,4} but they are afebrile. Within 24 hours or so, ataxia usually progresses to recumbency with episodes of opisthotonus, teeth grinding, nystagmus, and extensor rigidity of the limbs. Tactile stimulation readily induces seizures. Dorsomedial strabismus is quite characteristic. Coma and death follow fairly quickly, although occasional animals survive, usually to be left blind and demented. Cattle, sheep, and goats⁵ are responsive to treatment with thiamine early in the clinical course. The electroencephalographic features of the experimental disease in sheep and cattle have been described,⁶ as have the abnormalities in visual-evoked potentials in spontaneous cases.⁷

Ruminants with PEM have a diffuse encephalopathy. Postmortem examination of an advanced case will show spectacular CCN, which will explain the animals' blindness and seizures. However, it is important to appreciate that affected animals are recumbent and opisthotonic not as a consequence of this cortical injury but because of aberrations of cellular respiration in neuronal populations of the brain stem. These changes may not be expressed as a morphological change that the histopathologist can identify.

Gross pathological changes are often striking and frequently diagnostic in PEM. In typical fatal cases, the brain is swollen, resulting in flattening of gyri with subsequent narrowing of sulci. There may be tentorial herniation and coning of the cerebellar vermis. If the clinical course of CNS disease has lasted for a few days, the dorsal surface of the cerebral cortex is discolored yellowish tan, and this can be appreciated if it is compared with the cerebellar cortex, which (apart from areas that herniate) is unaffected. If PEM is severe, the cerebral cortex is soft to palpation, and transverse section reveals bilateral zones of cortical necrosis that appear yellow to tan and are friable compared to unaffected areas of cortex. This will also be apparent after formalin fixation. The parietal-occipital areas of the cerebrum are most affected, usually dorsally and dorsolaterally but sparing the cingulate gyrus adjacent to the longitudinal cerebral fissure and the major component of the rhinencephalon (olfactory peduncle, pyriform lobe, parahippocampal gyrus, and hippocampus). The areas of CCN can be identified by autofluorescence under ultraviolet light⁸ of fresh or formalin-preserved tissue. This is apparently a consequence of lipoidal material within macrophages that, when degraded, becomes autofluorescent,⁹ although others have related this autofluorescence to a high-molecular-weight, collagen-like material.¹⁰ Bilateral yellowish areas of necrosis in the caudal colliculi (and elsewhere in the brain stem) are also identified by this technique.

Microscopic changes are most dramatic in the cerebral

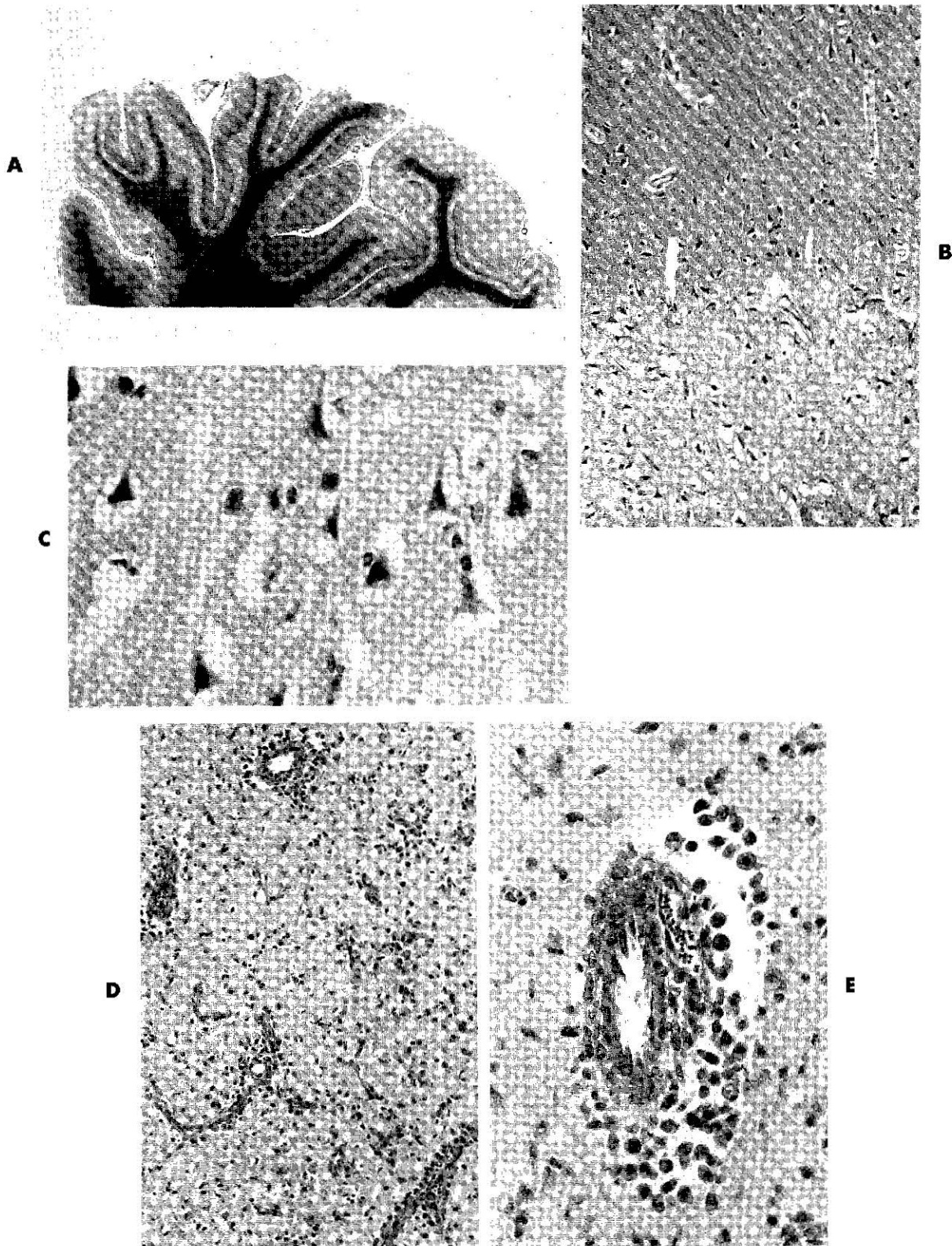


Fig. 5-48. Thiamine deficiency encephalopathy, cow. **A**, Laminar cerebrocortical necrosis. (H&E, $\times 3$.) **B**, Cortical necrosis from **A**: Note superficial dense, compact neuropil and deeper, pale rarified neuropil. (H&E, $\times 140$.) **C**, Contracted ischemic neurons with perineuronal astrocytic swelling. (H&E, $\times 560$.) **D**, Degeneration of cerebral cortex with neovascularization and intense macrophage activity. (H&E, $\times 140$.) **E**, Perivascular macrophages, cerebral cortex. (H&E, $\times 350$.)

cortex (Fig. 5-48). Segments of the superficial laminae are often intensely eosinophilic, and this is emphasized by the sponginess of the neuropil in the deep laminae—what Bestetti and Fankhauser¹¹ have called compact necrosis and edema necrosis. In the latter, there is pronounced pericapillary and perineuronal vacuolation and a spongy quality to the neuropil, all manifestations of intra-astrocytic edema. Junctional white matter may show mild ballooning of myelin sheaths. In both superficial and deep cortical laminae, individual or laminar groups of neurons become contracted with intensely acidophilic cytoplasm and basophilic pyknotic nuclei. With progressive nuclear karyorrhexis and cytoplasmic pallor, neurons are converted to ghosts that fade and disappear. Neuronal necrosis at first attracts a few polymorphonuclear cells into the neuropil and, about 24 hours later, macrophages from the leptomeninges and venules (often pericytes). With tissue liquefaction, gitter cell formation is soon evident as is the hyperplasia of capillaries, which have prominent, swollen endothelia. With time, a line of separation forms within the midcortex, usually at the junction of eosinophilic and vacuolar laminae. Removal of necrotic debris by macrophages sometimes leaves a cystic cavity encircled by reactive astrocytes. In exceptionally severe cases, there is total necrosis of affected cerebral cortex with leptomeninges covering the naked corona radiata (Fig. 5-49). In such cases, tissue loss results in a passive dilation of the lateral ventricles.

Changes in the brain stem are more subtle. Degeneration begins with spongiosis of the neuropil (which produces pallor), vascular endothelial hypertrophy, and small areas of hemorrhage. This progresses to spotty neuronal necrosis, spheroid formation, and a light, diffuse gliosis. Such changes are found consistently in the caudal colliculi and, in some cases, in the lateral geniculate nuclei and the oculomotor and vestibular nuclei. In a minority of cases, there is necrosis, loss of cerebellar Purkinje cells, and some depletion of granule cell neurons. These latter changes may be ischemic, following brain swelling and cerebellar herniation.

Ultrastructural studies of natural cases of PEM have been recorded in sheep, calves, and goats,^{4,11,12} and Morgan¹³ has compared the changes with those of the encephalopathy of Amprolium poisoning in lambs, a thiamine antagonist that in many ways simulates PEM. The earliest alteration in the natural disease is a hydropic swelling of neuronal satellite and interstitial astrocytes,¹² followed by neuronal necrosis of energy-deprivation type with ribosomal loss, distention and rupture of mitochondria, and Golgi swelling. Changes in the Amprolium-poisoned lambs followed the same sequence¹³ but were also marked by hemorrhages, probably due to megakaryocyte degeneration and thrombocytopenia.¹⁴

In cattle, sheep, and goats, thiamine is supplied by the synthetic activity of rumenal microbes, and a state of thiamine deficiency is believed to be due to thiamine-destroy-

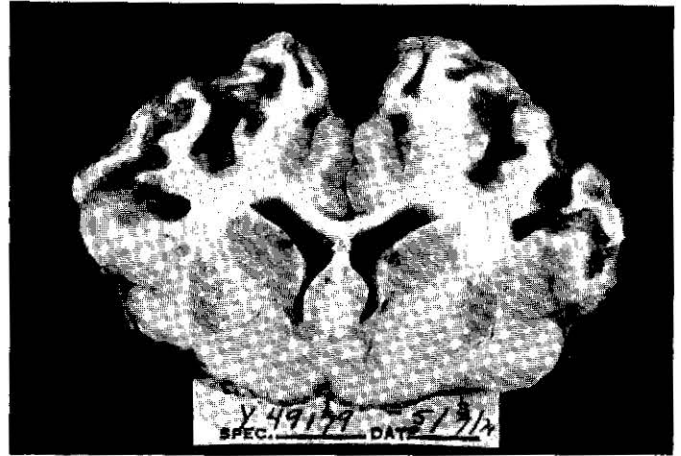


Fig. 5-49. Chronic thiamine deficiency encephalopathy, cow. Extensive loss of the dorsal and lateral cerebral cortex, leaving naked corona radiata and widened sulci. Note sparing of cingulate cortex.

ing enzymes acting within the gastrointestinal tract. The source of these enzymes is unclear. Whereas PEM can be produced by feeding bracken fern and other plants known to have thiaminase activity,¹⁵ such do not appear to be involved in most natural cases of the disease. Some episodes of PEM associated with moldy feed^{3,4} have prompted studies of pasture and alimentary fungi. Thiaminase activity has been found in the bacteria *Clostridium sporogenes* and *Bacillus thiaminolyticus*,^{16,17} but their role in the disease is not established¹⁸ and has been questioned.^{19,20} Rather, PEM may result from a change in the normal resident rumen microflora. Dietary composition most commonly associated with the development of the disease is high levels of concentrates or low quantities of roughage.²¹ Episodes of PEM have been associated with specific nutritional factors, including high levels of dietary carbohydrate (grain), molasses and urea²² (although the role of thiamine deficiency in this syndrome has been questioned¹⁵), cobalt deficiency,^{23,24} and, in particular, elevated sulfates.^{25,26,27} These various factors may influence the rumenal flora by favoring thiaminase-producing populations and perhaps also by diminishing populations that produce thiamine. A state of thiamine deficiency, resulting from alimentary thiaminase-producing microorganisms (in ruminants), should be viewed as a dynamic balance between available thiamine and thiamine-degrading activity. In animals that succumb, insufficient levels of the vitamin are available for crucial metabolic activity in the neuraxis; the corollary is that many clinically normal herdmates also have high levels of rumenal and fecal thiaminase activity.¹⁶ In this disease, the enzyme is designated thiaminase type 1.²⁸ Thiamine degradation products probably compete with intact thiamine, thereby exacerbating the deficiency.

Thiamine, mainly as thiamine diphosphate (pyrophosphate), has an important role as a coenzyme in carbohydrate metabolism, both in the tricarboxylic acid cycle and the

pentose pathway.²⁹ Thiamine requirement varies with animal species, metabolic activity (pregnancy, lactation), and feed intake; ruminants may often be on the borderline of deficiency.³⁰ Inhibition of carbohydrate metabolism in thiamine deficiency results in elevated levels of blood lactate, pyruvate, and oxoglutarate and lowered erythrocyte transketolase activity. The deficient state has general effects on metabolic activity beyond the neuraxis, and subclinical deficiency can reduce the growth rate of weaned sheep.³¹ There are also specific effects upon the CNS (described previously) that terminate in neuronal necrosis of energy-dependent type and distribution. It is noteworthy that the early morphological derangement is not in the cerebrocortical neuron but in its satellite cells. Presumably it is at this preliminary stage that the disease is amenable to thiamine therapy. In animals that succumb, there are significantly lowered levels of thiamine in the brain and liver.³²

Unfortunately, in some cases, the association between thiamine deficiency and PEM is less clear than all this would infer. Investigations of the unique form of PEM associated with molasses and urea-based diets have shown that in these animals, brain and blood thiamine levels are not reduced.²² Subsequently, an increasing number of studies have associated episodes of PEM with high levels of dietary sulfur, sulfates, or sulfides.^{25-27,33,34} Many of these reports have questioned the role of thiamine in PEM; in some, evidence of thiamine deficiency in the tissues of affected animals has been lacking. In part of an intriguing study, lambs were fed high levels of sulfur with or without additional levels of vitamin B₁. Increased thiamine appeared to prevent the development of clinical signs of PEM but did not fully preclude lesion development.³⁴ If we are to understand this metabolic encephalopathy, the relationship between these two nutritional factors must be clarified.

Thiamine deficiency encephalopathy is well recognized in **cats** and **dogs** and in **foxes** (Chastek paralysis) and **mink**. In cats, an early phase of anorexia and occasional vomiting is followed by a characteristic neurological disorder. There is a vestibular ataxia, pronounced pupillary dilation, and seizures, in which apparent disorientation produces marked ventroflexion of the head and neck, causing the animal to roll up into a ball. If thiamine is not provided, affected cats progress to prostration, opisthotonus and spasticity, coma, and death. The clinical course is similar in dogs, with an initial period of depressed growth in young animals, anorexia, and an abrupt and brief neurological disorder or, in some, sudden death.³⁵ Neurological signs are depression, ataxia, paraparesis, and sometimes seizures. As in ruminants, lactate and pyruvate are elevated, and transketolase is depressed.³⁶

At postmortem examination in deficient cats, dogs, and



Fig. 5-50. Thiamine deficiency encephalopathy, cat. Petechial hemorrhages in the caudal colliculi and vestibular nucleus.

other carnivores, grossly visible petechial hemorrhages are to be found bilaterally and symmetrically in brain stem nuclei (Fig. 5-50). The caudal colliculi are most faithfully affected, but the lateral geniculate, medial vestibular, oculomotor, habenular and other nuclei may also be involved.³⁷⁻³⁹ Occasionally, basal nuclei, the cerebral cortex, and the cerebellar vermis are affected also. Microscopically, the affected nuclei contain sharply defined areas that are pallid from edema,⁴⁰ are sprinkled with fresh hemorrhages, and contain prominent capillaries and venules with swollen endothelial cells. Vascular dilation and hemorrhage is more prominent in the carnivore than in the brain stem lesion in ruminants with PEM. The nucleus is gliotic and individual shrunken, degenerate neurons and swollen axons can be found. Extensive necrosis and cavitation is much less common here than in the cerebrocortical lesion in deficient cattle and sheep.

Thiamine deficiency encephalopathy in cats (and in farmed foxes and mink) usually results from a fish diet that is rich in thiaminase enzymes. In the 1930s, it was recognized that feeding raw carp to foxes would produce Chastek paralysis, and many types of fish have since been incriminated.³⁷ Thiamine can also be destroyed by the excessive heating of proprietary canned foods or cooking of meat,⁴¹ and this is the usual association with deficiency in dogs. Unlike the ruminants, carnivores are dependent upon their diet for their supply of this vitamin. Cats and dogs also develop thiamine deficiency if they consume meat preserved with sulfur dioxide.⁴²

Thiamine deficiency encephalopathy has been studied in **rodents** by means of dietary deficiency compounded by the administration of the thiamine antagonist pyriethamine.^{43,44}

References are on page 341.

Hereditary, familial, and idiopathic degenerative diseases

LEUKODYSTROPHIES, HYPOMYELINOGENESIS, SPONGY DEGENERATION, AND RELATED DISORDERS

Introduction—terminology

Leukodystrophies

- Dalmation dog leukodystrophy
- Alexander's disease—fibrinoid leukodystrophy
- Leukodystrophy of miniature rabbits
- Afghan hound myelopathy
- Miniature poodle demyelination
- Rottweiler leukoencephalomyelopathy
- Charolais cattle progressive ataxia

Hypomyelination

- Border disease of lambs
- BVD hypomyelination in calves
- Angus-Shorthorn, Jersey, Shorthorn and Hereford calves
- Congenital tremor in piglets
- Dogs—Springer Spaniel, Samoyed, Chow, Weimaraner, Lurcher, Bernese Mountain dog, Dalmatian
- Cats

- Mice, Rats, Hamsters

Spongy degeneration

- Spongy degeneration in white matter: dog, cat, fox, cow, sheep, mouse, rat, rabbit
- Spongy degeneration in gray matter: dog, cat

Introduction—Terminology

In this section, we have drawn together a group of diseases characterized by abnormalities of central myelination that have been variously designated as leukodystrophies, hypomyelinating disorders, or spongy degenerations. In most cases that will be discussed, the underlying derangement directly or indirectly affects the oligodendrocyte and is reflected in the production of CNS myelin of diminished quantity or quality or perhaps both. Many of these diseases are inherited and are manifest from or shortly after birth. A few are caused by viruses, but in this instance the agents are acting as teratogens of the developing fetal nervous system. Consequently, we prefer to present these conditions here, rather than in the chapter devoted to infectious diseases of the CNS, for the derangements they produce mimic those of genetic or toxic etiology.

The term **leukodystrophy** is used widely in human neuropathology and embraces a group of CNS white matter disorders that are clinically, pathologically, and biochemically diverse. In the most general sense, the term dystrophy implies abnormal nutrition, and it appears in a few classical neurological diseases, such as muscular dystrophy and neu-

roaxonal dystrophy. The leukodystrophies can be viewed as disorders of myelin synthesis and maintenance, and they are sometimes called **dysmyelinating diseases**.¹ As biochemically abnormal myelin is prone to degeneration (and for other reasons), primary demyelination may be seen in the leukodystrophies. It is important to make a distinction between these diseases and the classical demyelinating disorders, such as multiple sclerosis and canine distemper, which are thought or known to be acquired rather than inherited, and which involve destruction of normal white matter myelin. There are further points of distinction:

1. The leukodystrophies sometimes involve both CNS and PNS myelin.
2. In the leukodystrophies, white matter involvement is often bilateral and symmetrical, but is regional. Thus, for example, although cerebral hemispheric white matter may be affected, white matter in the brain stem or cerebellum may be largely intact.
3. In advanced leukodystrophic lesions, there is considerable axonal necrosis.
4. Lymphoplasmacytic inflammatory changes are not anticipated in the leukodystrophies.

Both familial and sporadic forms of leukodystrophies are recognized in humans. For some, the underlying metabolic disorder is now established, which only emphasizes their pathogenetic diversity. Historically, each member of this group of diseases evolved as a nosological entity by virtue of the clinical presentation, together with the characteristic white matter alterations found at necropsy. A few were named eponymically. For some, a classification of sorts was based upon the histochemical quality of the degraded myelin (hence **metachromatic** and **sudanophilic leukodystrophy**). Contemporary studies have established that globoid cell leukodystrophy and metachromatic leukodystrophy are lysosomal storage diseases, and we have discussed them in that section of the book. Neonatal and the X-linked form of human **adrenoleukodystrophy** are peroxisomal disorders.^{2,3} Alexander's disease is characterized by the prolific formation of Rosenthal fibers within astrocyte processes and could be viewed as an intermediate filament disorder;⁴ however, there are also white matter changes, and the term **fibrinoid leukodystrophy** has been applied.

For several of the human leukodystrophies, clinical variants (such as neonatal, juvenile, and adult forms) are recognized. Within **Pelizaeus-Merzbacher disease**, there is an infantile form (so-called Seitelberger variant), which is marked by the diffuse lack of myelin and an accompanying astrocytosis. We would designate such a disorder as CNS

hypomyelination, analogous to several conditions in animals that are reviewed later in this section, and some authors do view the disorder fundamentally as a myelin aplasia.⁵ Thus hypomyelinating diseases can be considered as a subgroup of the leukodystrophies, perhaps representing one end of the spectrum. It is interesting that both terms (hypomyelination, leukodystrophy) are used in veterinary medicine but only the latter for human diseases. Finally, Canavan's disease of humans—one form of **spongy degeneration** of white matter—is also usually classified as a leukodystrophy, and we have concluded this section with a discussion of the variants of spongy degeneration seen in animals. Some would expand the list even further¹ to include the disorders of amino acid metabolism (we discuss maple syrup urine disease in cattle here) and other conditions.

Leukodystrophies

At this point, we first address the individual syndromes recognized in animals that have been named, or perhaps could be viewed, as leukodystrophies. They are followed by those groups that have been designated hypomyelinating diseases or spongiform degenerations.

Some leukodystrophies that occur in animals are comparable to their human counterpart, for example, globoid cell leukodystrophy of dogs and mice, whereas others, such as the leukodystrophy of Dalmatian dogs, are novel. In 1983, the spectrum of animal leukodystrophies was reviewed by Fankhauser and Vandeveld.⁶ As is true for many neurological conditions, most occur in the dog. Bjerkås⁷ has described a **leukodystrophy of Dalmatian dogs** bred in Norway. Clinical disease, occurring in dogs of both sexes, begins between 3 and 5 months of age. Neurological signs are of visual deficits and a pelvic limb ataxia that slowly progresses to involve forelimbs also. Chronic disease has not been studied, as affected dogs were euthanized within 4 months of the onset. At necropsy, there are bilateral grayish depressed areas in the white matter of the centrum semiovale and corona radiata of the cerebral hemispheres. In some cases these progress to complete cavitation of the tissue, but with sparing of U fibers. Gray lucent areas may be found in the caudate nucleus and putamen also. Microscopic changes begin with diffuse loss of stainable myelin and initially good preservation of axons. Many granular macrophages are found in the pallid white matter and as perivascular sleeves. Reactive astrocytosis is pronounced with progressive myelin removal and at the margins of cavities. Microscopic lesions are most consistently found in the centrum semiovale, internal capsule, optic nerves, and spinal cord. However, as is seen with some of the human leukodystrophies, lesions are not found uniformly in the neuraxis. In affected Dalmatians, the midbrain, cerebellum, and medulla oblongata are normal. The myelin-like nature of the inclusions has been shown by EM. They are sudanophilic and non-metachromatic. Spinal roots and nerves are normal. Breeding studies are consistent with an autosomal,

recessive pattern of inheritance. The biochemical deficit has not been defined.

Alexander's disease is a rare, progressive neurological human disorder. The typical form, which is infantile, is marked clinically by megalencephaly, psychomotor retardation, and spasticity. Characteristic pathological changes are a grayish discoloration of the white matter, especially of the prosencephalon, and ventricular enlargement. Microscopically, there is evidence of widespread myelin pallor and the characteristic Rosenthal fibers throughout the CNS. These "fibers" are ovoid, variably sized, strongly eosinophilic hyaline bodies, disposed particularly below the pia mater and the ependyma, and around blood vessels in both gray and white matter. Their disposition in the glia limitans reflects the fact that these bodies are situated within the processes of astrocytes. By light microscopic examination they are GFAP negative but take the Luxol fast blue stain;⁸ ultrastructurally, they consist of electron-dense amorphous deposits⁹ that include considerable $\alpha\beta$ -crystallin with some GFAP and ubiquitin. In the original report of Alexander's disease, these structures were described as a fibrinoid degeneration of astrocytes. Together with the white matter abnormality, this disorder is sometimes designated a **fibrinoid leukodystrophy**. Typical cases (with onset during the first 2 years of life) show extensive myelin vacuolation and loss, and diffuse astrocytosis with some neuronal depletion in the cerebrum and thalamus.

Rosenthal fibers are thought to reflect a metabolic abnormality in astrocytes. They are seen occasionally in humans in other settings in which there is reactive astrocytosis, and in astrocytomas. It is controversial whether all of the presumed metabolic encephalopathies with late childhood or adult onset, in which Rosenthal fibers are found, qualify as cases of Alexander's disease.¹⁰

Rosenthal fibers have very rarely been observed in animal neuropathology (Fig. 5-51). In 1979, McGrath¹¹ described a unique encephalopathy in two littermate male black **Labrador retriever dogs**. At approximately 6 months of age, these two dogs developed a pelvic limb paresis and ataxia, a basewide stance, exercise intolerance, and, in one, an altered sensorium. They were euthanized after clinical courses of 3 and 10 months. In both, there was a grayish quality to the cerebral white matter that, microscopically, was pallid and vacuolated. Rosenthal fibers encircled blood vessels in the affected white matter. Astrocytic gliosis was found in the cerebrum, basal nuclei, and brain stem nuclei. Sorjonen, Cox, and colleagues^{12,13} described a novel myeloencephalopathy in a **Scottish Terrier dog**. Three male littermates of this animal had been euthanized before 6 months of age because of severe neurological abnormalities. Fortunately, this fourth male was studied clinically and pathologically. A progressive tetraparesis, ataxia, and head tilt began at about 6 months of age. Seizure-like activity also developed. Euthanasia at 9 months of age revealed widespread Rosenthal fiber formation throughout the brain

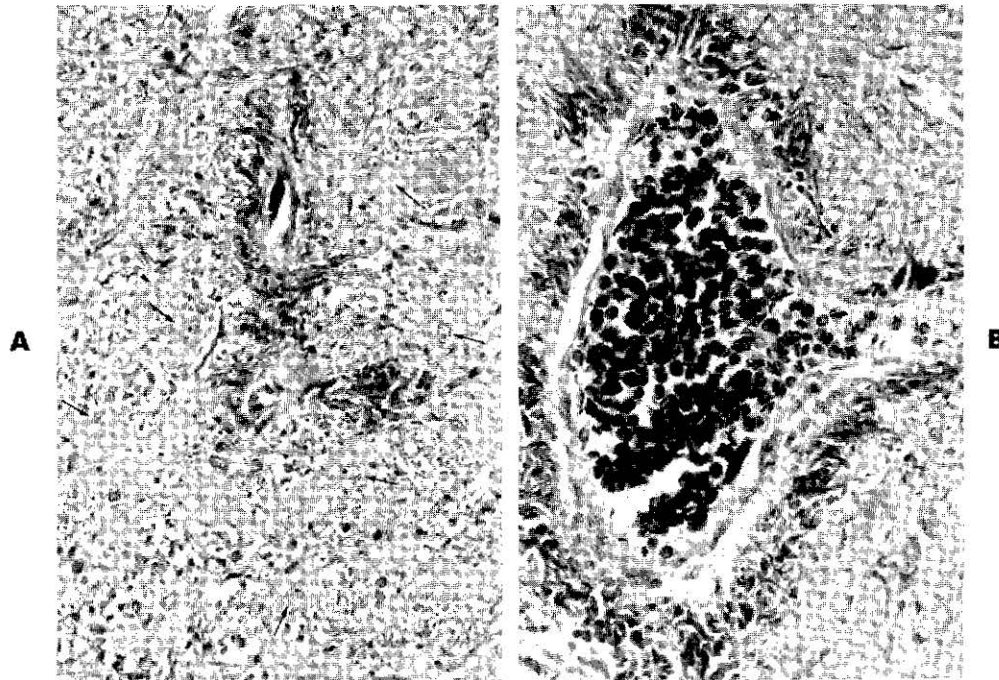


Fig. 5-51. Alexander's disease, dog. **A**, Perivascular Rosenthal fibers and hypertrophic astrocytes (arrows), medulla. (H&E, $\times 350$.) **B**, Detail of Rosenthal fibers. (H&E, $\times 350$.)

and spinal cord. There was some diminution of myelin staining, particularly in the corona radiata, cerebellar, and spinal cord white matter. Astrocytosis was conspicuous through the cerebral white matter, brain stem, and spinal cord. Ultrastructurally, the Rosenthal fibers consisted of granular osmiophilic deposits closely associated with glial filaments.¹³ A further case has been reported in a 6-month-old **Miniature Poodle**.¹⁴

Based on their early onset and the nature of the pathological changes, these episodes can be viewed as a syndrome in the dog like Alexander's disease. Fankhauser and associates⁸ have also described widespread Rosenthal fiber formation with spongy white matter in an emaciated, tetraplegic, 4-year-old **sheep**. Reported as an encephalopathy with Rosenthal fiber formation, this case could be viewed as Alexander's disease of late onset, akin to the adult-onset form seen sometimes in humans.

Vandeveldt and Fankhauser¹⁵ have reported a **leukodystrophy of miniature rabbits**. The three female animals studied presented at about 10 to 12 weeks of age with a progressive course of pelvic limb ataxia and paresis to paralysis. All three animals were euthanized and examined postmortem. Although gross changes were lacking, histological examination revealed a widespread abnormality of CNS myelin. The tissue was pallid, rarefied, and astroglitic. The funiculi of the spinal cord were most severely affected, although the corpus callosum, optic tracts, thalamus, and medulla oblongata were significantly involved. Lesions extended into the spinal roots and peripheral nerves.

Histochemical stains did not clarify the nature of the leukodystrophy; axons were well preserved.

An acute spinal cord disease of **Afghan Hound dogs** has been recognized by McGrath since the early 1960s. Averill and Bronson¹⁶ have studied the disorder and provide evidence for a simple autosomal pattern of inheritance.

Affected dogs, equally males and females, often present around 6 months of age (range 3-13 months) with a rapidly progressive, symmetrical, spastic paraparesis and ataxia of the pelvic limbs. Some show a bunny-hopping type of gait.¹⁷ Dogs are commonly paraplegic in 7 to 10 days with stiff thoracic limbs and trunk weakness; some progress to tetraparesis or tetraplegia. Spinal reflexes and tone are increased, except in rare cases in which gray matter involvement ensues. Pelvic limb hypalgesia is common because of the extensive funicular white matter lesion. Nociception utilizes a number of tracts, including the classic spinothalamic tract. In some cases a sensory line can be detected.¹⁶ The CSF may be normal or show elevated levels of protein.

Pathological changes, symmetrical and bilateral, are remarkable (Fig. 5-52). In the spinal cord, cribriform change affects all funiculi in the midthoracic segments, resulting in extreme softening and grayish discoloration. In its most extreme form, the tissue is cavitated and is most difficult to handle and maintain intact. Rarefaction extends cranially to about the midcervical segments, tapering to involve often only the dorsal and/or ventral funiculus. Caudal extension tapers down to the ventral funiculus and extends to about L5 (see diagram in Averill and Bronson¹⁶). Fasciculus pro-

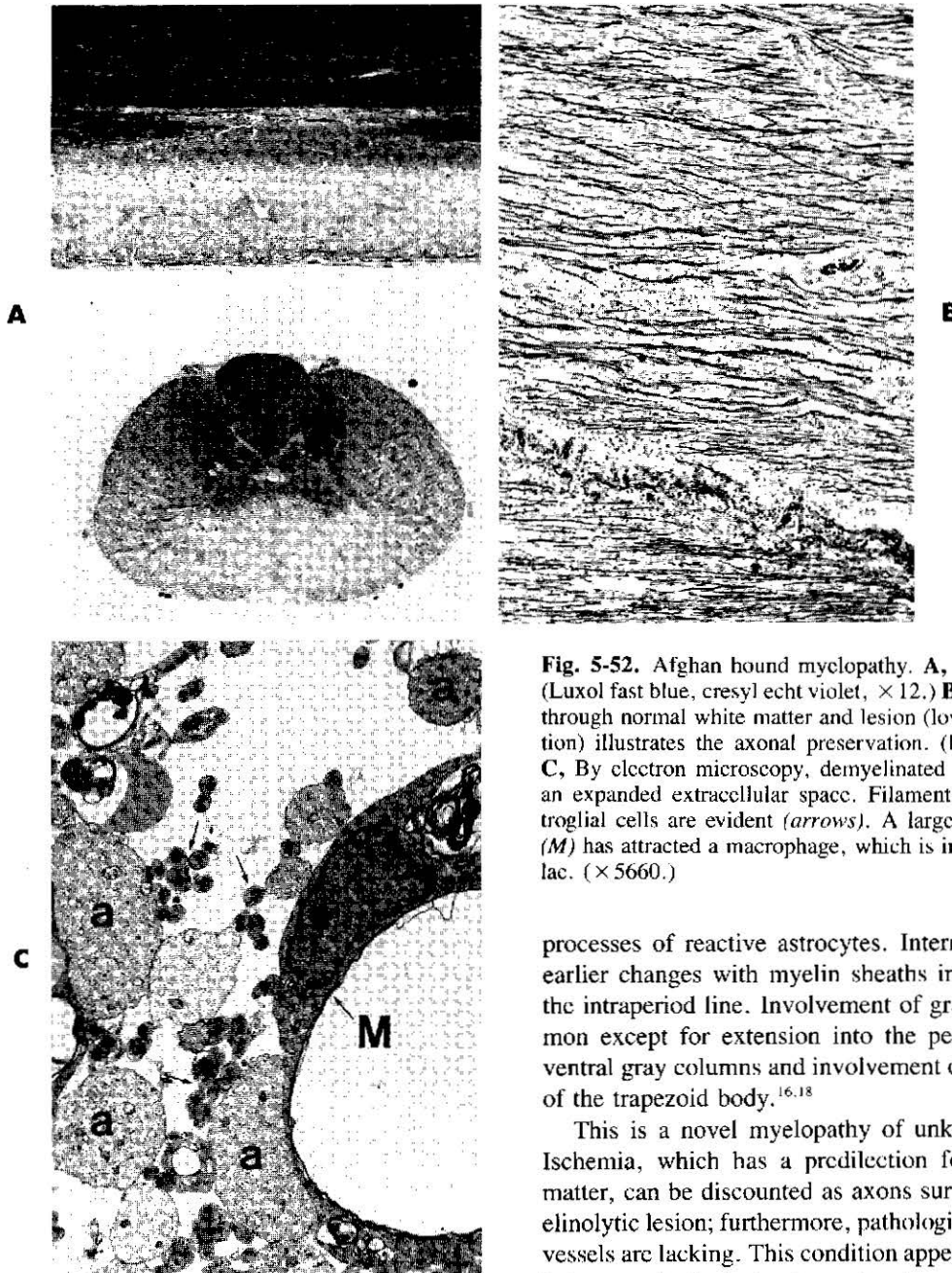


Fig. 5-52. Afghan hound myelopathy. **A**, Thoracic spinal cord. (Luxol fast blue, cresyl echt violet, $\times 12$.) **B**, Longitudinal section through normal white matter and lesion (lower middle of illustration) illustrates the axonal preservation. (Holmes silver, $\times 90$.) **C**, By electron microscopy, demyelinated axons (*a*) are seen in an expanded extracellular space. Filament-rich processes of astroglial cells are evident (*arrows*). A large, free loop of myelin (*M*) has attracted a macrophage, which is internalizing the lamellae. ($\times 5660$.)

prius is usually spared. Microscopic lesions vary from mildly loosened white matter with vacuolated myelin sheaths to extreme cribriform change, depletion of normal neuroglial elements, redundant blood vessels, and numerous gitter cells filled with degenerate myelin. Examination of more cranial cervical or more caudal lumbar segments reveals surprisingly little Wallerian degeneration, reflecting the remarkable capacity for axons to survive in this lesion, often in a fully demyelinated state.¹⁸ These can be demonstrated in silver-stained paraffin sections, where clusters of fibers are seen. Electron microscopy provides greater detail; in cavitated areas, naked fibers are buoyed up by the

processes of reactive astrocytes. Intermediary areas show earlier changes with myelin sheaths intact but splitting at the intraperiod line. Involvement of gray matter is uncommon except for extension into the peripheral portions of ventral gray columns and involvement of the dorsal nucleus of the trapezoid body.^{16,18}

This is a novel myelopathy of unknown pathogenesis. Ischemia, which has a predilection for spinal cord gray matter, can be discounted as axons survive within the myelinolytic lesion; furthermore, pathological changes in blood vessels are lacking. This condition appears to lie somewhere between a leukodystrophy and a demyelinating disease of peculiar limited topography. Averill and Bronson pursued an analogy with human subacute combined degeneration but could provide no evidence of vitamin B₁₂ deficiency. Nevertheless, striking pathological similarities exist between this myelinolytic disease in Afghan hounds and subacute combined degeneration as induced in monkeys by B₁₂ deficiency.¹⁹

A very rare syndrome, described as a demyelinating disease, has been seen in the **Miniature Poodle dog**. Douglas and Palmer²⁰ reported one case in a 9-week-old pup that presented with a progressive spastic tetraplegia. McGrath²¹ studied two clinically similar cases at 3 and 5 months of age. These two pups had the same dam and sire but were

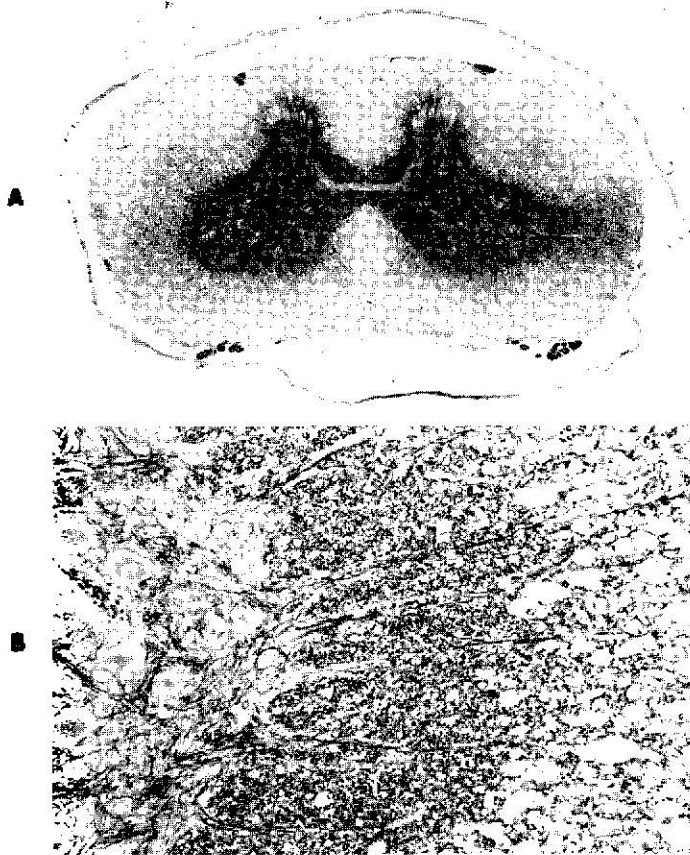


Fig. 5-53. Poodle dog demyelinating disease. **A**, Caudal cervical spinal cord. Myelin pallid except in fasciculus proprius. Note normal staining of spinal roots. (Luxol fast blue, cresyl echt violet, $\times 10$.) **B**, Ventral horn (left), myelinated fasciculus proprius and unstained more peripheral fibers. (LFBCEV, $\times 140$.)

not littermates. Two cases have been observed at Cornell over the course of approximately 30 years.

At postmortem examination, the spinal cord white matter is spongy and translucent. There is extensive loss of myelinated fibers in the spinal cord and midbrain. Smaller foci are found extending from the corpus callosum to the pyramids, mainly in the brain stem. The spinal cord lesions are most dramatic (Fig. 5-53). There is a bilateral, symmetrical cribriform degeneration of white matter that spares the fasciculus proprius. Silver stains reveal at least some degree of axonal integrity, attesting to the myelinolytic nature of this disorder. Microscopically it has much in common with the Afghan myelopathy, differing in the topographic distribution of the lesions.¹⁸

A chronic **leukoencephalomyelopathy of the Rottweiler dog**, reported from several countries, has been studied most extensively in the Netherlands.²² Clinical data were available for 16 dogs, of which 11 were examined postmortem. Progressive ataxia involving all four limbs began insidiously between 1.5 and 3.5 years of age, in both male

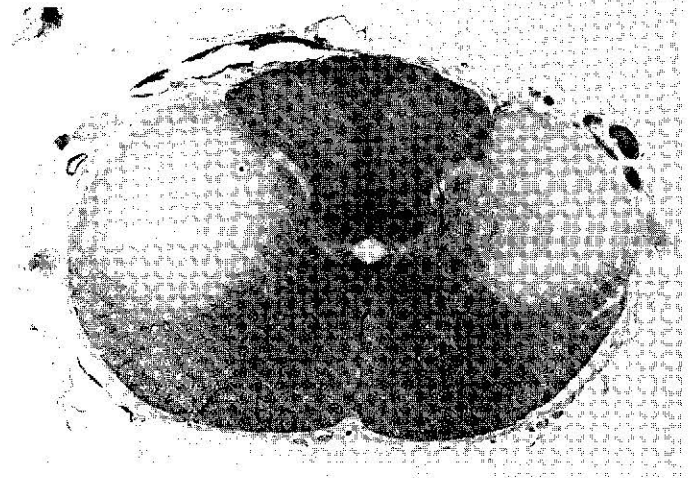


Fig. 5-54. Rottweiler leukomyelopathy. Bilateral lesion in the lateral funiculus, cervical spinal cord. (Luxol fast blue, cresyl echt violet, $\times 10$.)

and female dogs. Signs of upper motor neuron paresis with proprioceptive deficits and ataxia were pronounced. An apparently identical syndrome has been recorded in Australia²³ and in two American Rottweilers.²⁴ Interestingly, these latter two dogs were related with a common grandsire, who was affected with neuroaxonal dystrophy (NAD), a syndrome also recently described in this breed. Clinically this leukoencephalomyelopathy must be differentiated from neuroaxonal dystrophy and from cervical vertebral malformation-malarticulation, which affects several large dog breeds, including the Rottweiler.²²

For all animals examined, CSF, radiography, and EMG studies have been normal. At autopsy, discrete, bilateral whitish areas are evident upon sectioning the cervical spinal cord. These areas involve the dorsal parts of the lateral funiculus and, less regularly, the dorsal funiculus. Microscopic examination reveals a more widespread demyelinating process, extending into the thoracic spinal cord; rostrally lesions are found in the brain stem, caudal cerebellar peduncles, pyramids, and optic nerves and tracts. Lesions are bilateral (Fig. 5-54) but show some degree of asymmetry. The midcervical spinal cord is most densely involved with primary demyelination, active phagocytosis of myelin debris, and a reactive astrocytosis. Occasional spheroidal or necrotic axons are observed, and from plastic embedded tissue there is an impression of some axonal depletion. Wallerian degeneration above and below the spinal cord lesions is minimal however, attesting by and large to axonal preservation. Some axons are invested by thin sheaths and are interpreted to indicate remyelination.

Pedigree analysis of the Dutch dogs did not elucidate the mode of inheritance, but considerable inbreeding was evident. The pathogenesis of this disorder is unknown. At this time it can be tentatively classified as a myelinolytic disease.

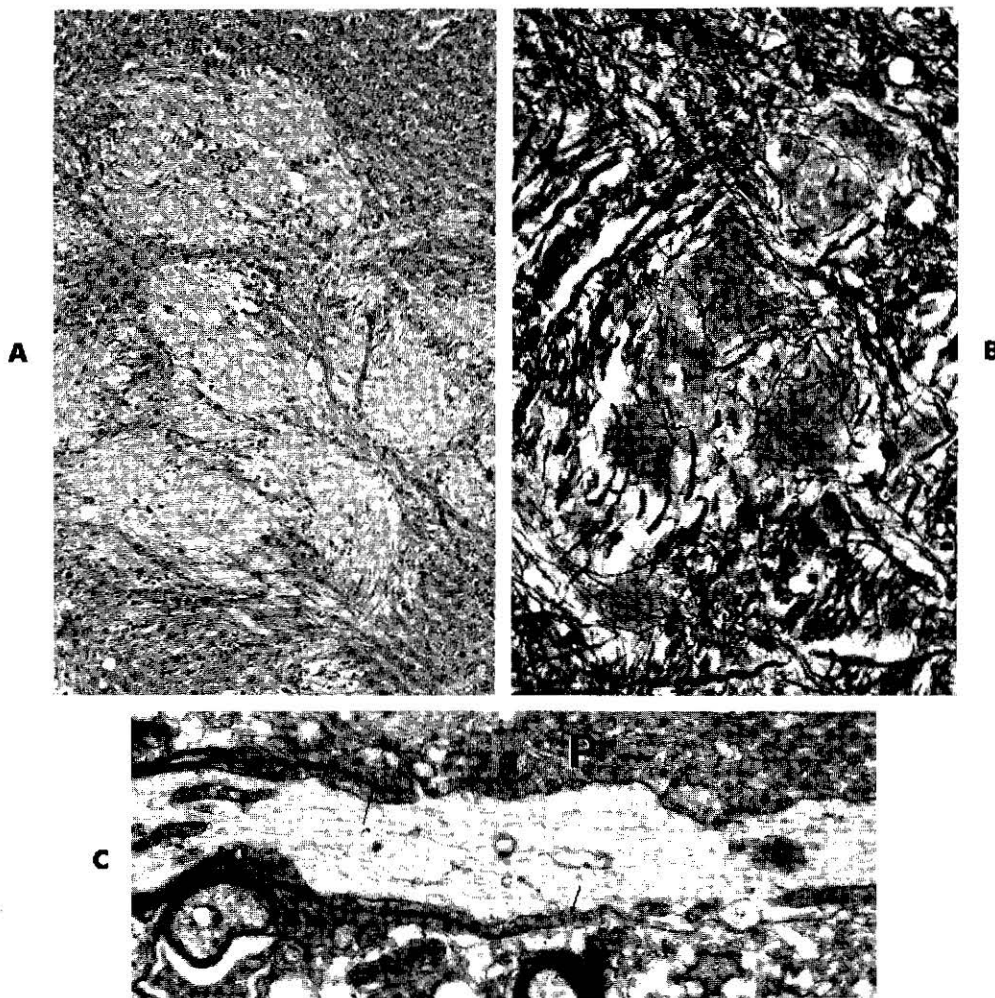


Fig. 5-55. Charolais ataxia. **A**, Multiple plaques in the internal capsule. (H&E, $\times 140$.) **B**, Axons traverse plaques. (Luxol fast blue-Holmes, $\times 350$.) **C**, In this electron micrograph of a myelinated axon, the paranodal loops are tapered and end asymmetrically (arrows). The node of Ranvier is widened and is abutted by cytoplasmic processes (*p*) from oligodendrocytes. ($\times 9930$.)

Several peculiarities must be reconciled: The signs do not begin until adulthood (mean 2.2 years) and are progressive, yet the neuropathological picture is one of repair of a prior demyelinating episode or episodes. Predominant involvement of one segment of the spinal cord (cervical) is reminiscent of the Afghan hound myelopathy, most conspicuous in the thoracic spinal cord.

Progressive ataxia of Charolais cattle is a novel neurological disorder that has been studied by Palmer and colleagues^{25,26} in the United Kingdom. Clinical signs of a stiff, stumbling gait, usually in the pelvic limbs, begin between 1 and 2 years of age; both sexes are affected. Pelvic limb ataxia becomes progressively more severe with increasing periods of recumbency and difficulty in rising. By this time, mild spasticity and ataxia of the forelimbs are usually evident. If the animal is excited, a head nodding may develop; otherwise, affected cattle are bright and alert and lack cerebral signs. A characteristic feature in the female is a rhythmic pulsatile pattern of urination.

There are no gross lesions in the nervous system. Microscopic findings are of numerous, sharply demarcated eosinophilic plaques within the white matter of the CNS (Fig. 5-55, *A, B*). Plaques are widely disseminated but are most abundant in the cerebellar medulla and folia, internal capsule, corpus callosum, optic tract, and the spinal cord (lateral and ventral funiculi). Plaques are homogeneous to slightly granular, contain few glial cell nuclei, and may be marked by vacuolation at their margins. Silver stains show that they are traversed by axons. Some plaques show a perivascular disposition. The normal myelinated tissue is only mildly gliotic but angular, hypertrophic oligodendrocytes are present. Ultrastructural studies²⁷ reveal changes that may be unique in animal and human neuropathology. The plaques consist of single or multiple axons with a disorder of paranodal myelin. Nodes of Ranvier are widened, and in the place of normal paranodal loops are whorls of slender processes that encircle the axon (Fig. 5-55, *C*). These processes emanate from hypertrophic tongues of oligodendrocyte cy-

toplasm; contiguity of the two has been shown. Myelin figures may be found in paranodal areas but fail to incite a histiocytic response. Oligodendrocyte somata are enlarged and contain mitochondria in excess. A single case report of a white matter disorder in a 13-year-old child describes somewhat similar oligodendrocytes with aberrant cytoplasmic processes.²⁸

This singular disorder in Charolais cattle, a breed of French origin but now found worldwide, is presumed to have an inherited basis. A primary oligodendrocyte disorder is supported by the electron microscopic findings, and Cordy²⁹ has used the term oligodendroglial dysplasia, which seems most reasonable. Hence this disorder can be viewed as a gliopathy, resulting in a leukodystrophy. The late clinical onset (usually at 1-2 years) and progressive course, well after CNS myelination should be completed, is most peculiar. A further disparity, but not unique to this neurological disease, is the poor clinicopathological correlation between lesion distribution and the clinical deficits.³⁰

Hypomyelination

In the congenital **hypomyelinating diseases**, oligodendrocytes are diminished in number or may be quantitatively normal but functionally incompetent. The development of subnormal CNS myelination^{31,32} could result from:

1. Failure of glial progenitors to generate an adequate pool of competent oligodendrocytes
2. Failure of differentiated cells to migrate through the neuropil to axons
3. Failure of oligodendrocytes to respond to the axonal message that triggers ensheathment and myelination
4. Premature oligodendrocyte death

Myelination is a complex, interactive process, and potentially the defect may not be oligodendroglial. Primary axonal abnormalities must be considered, including

1. Failure to reach the critical diameter for myelination
2. Failure to produce oligodendrocyte trophic factors that recruit these cells
3. Failure to initiate axon-oligodendrocyte association and ensheathment

Astrocytes are also intimately involved in the production of a normal myelin sheath and so are a further potential source of disorder.

The clinical expression of the leukodystrophies, which we have previously discussed, is usually delayed a few weeks or months after birth but then is progressive. In contrast, the hypomyelinating disorders are marked by whole-body tremors of variable intensity and persistence at or soon after birth. Typically the tremors worsen with excitement or stress; they subside with rest and disappear during sleep. Their pathophysiological basis must reside in the failure of normal myelin ensheathment of axons, and the observation of these signs in a neonate can fairly reliably be taken to indicate a state of diffuse hypomyelination. In some of these diseases, affected animals survive to maturity, and this is invariably associated with a progressive reduction of their

tremor. In such animals, there is further myelination of the neuraxis in the postnatal period, although myelin abnormalities remain, and sometimes the degree of clinical recovery is surprising.

Myelin formation is necessary for internodal insulation—limiting ion currents to the nodes of Ranvier—and for saltatory conduction (rapid movement of the impulse from one node to the next). In the hypomyelinated state, which is mostly a mixture of thinly and non-myelinated CNS fibers, it seems that some degree of axonal conductivity is possible but selectivity is lost, resulting in ectopic spread of the impulse to neighboring fibers.³¹ Perhaps with asynchronous conduction times, groups of lower motor neurons are not recruited together and a tremor results. Ablation studies in piglets with congenital hypomyelination pointed to the spinal cord as the source of the generalized, repetitive tremor activity.³³

It is important to distinguish between the clinical manifestations of severe cerebellar disease and diffuse neuraxial hypomyelination. Animals with cerebellar disorders may show a coarse head titubation but do not have a diffuse, whole-body tremor; conversely, myelin-deficient animals should not have balance deficits or dysmetria. Rarely (e.g., in congenital tremors type AI in piglets), there is both cerebellar injury and hypomyelination.

Congenital neurological disease associated with **hypomyelination** occurs in many domestic and laboratory animals. These disorders have a diversity of causes: Several are inherited (often X-linked); others result from in utero infections or intoxications. A diagnosis of hypomyelination (by whatever means) requires a knowledge of the normal patterns of myelination. In humans, MRI has proven to be a most useful clinical tool for evaluating the status of CNS white matter, whether for an evaluation of its potentially disordered development or in the acquired myelin diseases.^{34,35}

In 1959, a condition in **sheep** described as **hypomyelination congenita** or **Border disease** was reported in England.^{36,37} Affected lambs (some were in flocks on the border of England and Wales) manifest a novel clinical disorder of continuous, whole-body tremors. They were often noted to be smaller than unaffected lambs and also had an abnormally hairy and sometimes brown or black pigmented fleece. It is now established that Border disease results from transplacental infection of the fetal lamb with a pestivirus (family *Togaviridae*)³⁸ that has been named Border disease (BD) virus. The agent is closely related to two other pestiviruses, bovine virus diarrhoea (BVD) and hog cholera viruses. Pestiviruses can cross species barriers with relative ease,³⁸ resulting in both infection and disease. For example, BVD virus infection in pigs can produce a disorder resembling chronic hog cholera (swine fever).³⁹ In nature, exchange of virus between cattle and sheep⁴⁰ is probably common (other ruminants may also be involved⁴¹), and isolates are named BD or BVD virus on the basis of the species from which they are recovered. In all three animal species, in utero

infection and teratogenic effects are important in producing congenital CNS disease, whereas in cattle and sheep, persistent infection is involved in the more delayed manifestations of the infection. A pestivirus-contaminated orf vaccine administered to goats resulted in considerable reproductive failure (one possible expression of Border disease) and the transmission of infection to in-contact sheep and cattle.⁴²

There are a number of serologically distinct strains of all three pestiviruses that vary in their pathogenicity and effects on the host. Crucial to their teratogenic activities is the stage of gestation at which the embryo or fetus is infected, this bearing on organ development and immune competence. The progressive development of immune capacity in the later stages of gestation modulates and perhaps enhances fetopathic effects of the virus.³⁸ Viral strain and host genotype are also factors of importance. Border disease results from infection at around 30 to 80 days of gestation. Affected lambs have abnormalities of their skeleton, fleece, CNS, and other organs. The most severely affected lambs have severe, whole-body tremors that prevent their standing and suckling, and many die soon after birth unless attended to individually. In other lambs, tremors may be less severe; such cases commonly survive, and their tremor and ataxia slowly improve. At first, such lambs have an erratic, ataxic gait, sometimes hopping or jumping with the pelvic limbs. Typically, tremors abate during sleep.³⁶ Least-affected lambs are clinically normal, but they too are persistently infected with, and more or less tolerant to, BD virus.⁴³ They will give birth to further affected lambs and spread the infection laterally to in-contact sheep and cattle.⁴⁴ Sporadic cases of BD infection present in juvenile to adult sheep as ill-thrift, chronic diarrhea, and, at necropsy, ileoceccocolonic mucosal lesions.⁴⁵ Similar to the circumstances that prevail in BVD, most isolates of BD virus from hairy shaker lambs are non-cytopathic (when propagated in tissue culture), whereas sheep with the alimentary form harbor a cytopathic strain of the agent.

In sheep flocks with BD infection, the spectrum encountered is fetal deaths (reflected as infertility in the ewe), abortions (which may be associated with placental lesions⁴⁶), stillborn lambs, lambs with clinical Border disease, and subclinically affected lambs.⁴⁵ Aborted or stillborn lambs and viable lambs with BD are small, reflecting retarded growth in utero. In BD lambs, skeletal abnormalities include a shortened and domed cranium and a shorter, finer appendicular skeleton.⁴⁷ Fleece abnormalities (coarse, straight, hairy coats) result from aberrations of follicular differentiation: There is a hyperplasia and increased medullation (the presence of a central medulla) in the fibers of primary follicles, which are enlarged, and fewer than normal secondary follicles.⁴⁸ Affected lambs are frequently described as **hairy shakers**.

In BD, the brain and spinal cord weights are diminished, compared with controls,⁴⁷ but the body size of affected



Fig. 5-56. Hypomyelination, sheep. Normal brain on left. In the affected brain, white matter (especially corona radiata) is dull and gray. The lateral ventricles are dilated.

lambs is also proportionately reduced. Myelin deficits may be grossly evident with a loss of the normal distinction between gray and white matter (Fig. 5-56);³⁶ however, in any animal, such an evaluation may be hard to make during the first few weeks of life. Microscopically, the diffusely hypomyelinated CNS tissue is pallid and stains poorly or not at all with dyes for myelin sheaths (Fig. 5-57). Evidence of myelin degeneration and phagocytosis is lacking, but the myelin formed is chemically abnormal, with abnormal cerebrosides and cholesterol esters accumulating. These seem to invoke the production of antimyelin antibodies,⁴⁹ which, in surviving lambs, decline with neurochemical recovery.

In normal lamb fetuses, glial cell numbers in the white matter decline beyond gestational day 95, but they remain elevated in BD fetuses. Some of these interfascicular glial cells bear cytoplasmic lipid inclusions. Axonal preservation is normal and does not account for the lack of myelin formation. Lambs that show neurological improvement acquire a fuller complement of myelin⁵⁰ but still have less than normal. The PNS is unaffected.

Ultrastructural examination of classical BD white matter reveals hypomyelinated or amyelinated axons, often with an irregular contour that is normally seen just transiently before myelinogenesis is underway.⁵¹ The increased numbers of interstitial cells are microglia (Vaughn's type III glia), and they harbor a rich complement of endogenous neutral lipid vacuoles. Myelin sheaths are thin, often poorly or irregularly compacted with increased periodicity. In BD fetuses, the rate of myelination proceeds more slowly than in normal animals. Although the evolution of differentiated astrocytes and oligodendrocytes can be followed in BD fetuses, numbers of mature oligodendrocytes are reduced approximately 40% in diseased animals.⁵²

Infection in early fetal life with BD virus results in the dysplastic development of several tissues—bone, skin.

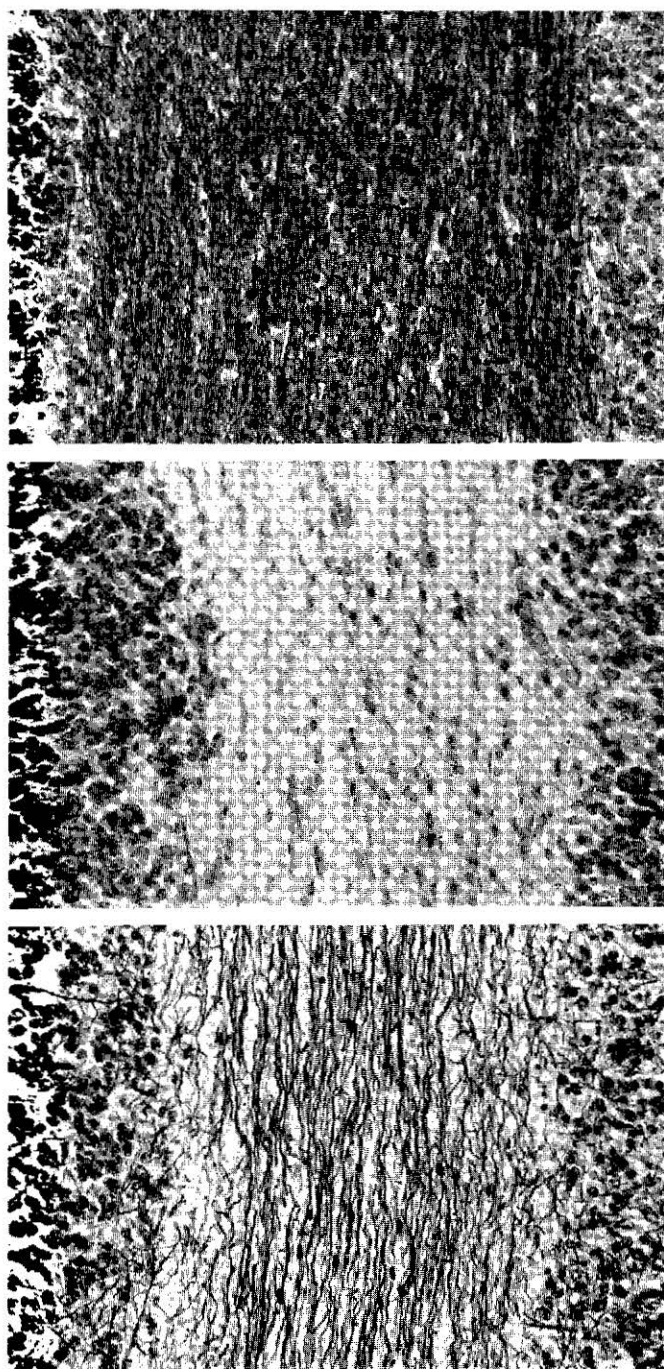


Fig. 5-57. Hypomyelination, sheep. A, Normally myelinated cerebellum. (Myelin stain, $\times 350$.) B, Hypomyelinated cerebellum. (Myelin stain, $\times 350$.) C, In the hypomyelinated cerebellum (B), axons are normal. (Romanes, $\times 350$.)

CNS—and in none is the mode of viral action clear. The simplest interpretation of the failure of normal CNS myelination is an effect of the BD virus on oligodendrocyte precursors or mature, differentiated cells. Blakemore has suggested that the hypomyelinogenesis may be a loss of “luxury function” (Oldstone’s concept) in which the infected

cell—here an oligodendrocyte—is viable but loses its functional capacity, in this case to form a normal myelin sheath on multiple CNS axons. This deficit may be evident only during times of growth when axonal extension would require a several-fold increase in myelin synthesis by each oligodendrocyte. The BD antigen has been detected by immunofluorescence in the CNS tissue of affected lambs,⁵³ although the number of infected cells is low.⁵⁴ In immunocytochemical studies, BD antigen was found in neurons, astrocytes, and oligodendrocytes, as well as in vascular endothelia and fibrocytes.⁵⁵ In tissue culture experiments employing fetal and adult ovine CNS, BD infection was reported to be common in astrocytes,⁵⁶ oligodendrocytes, neurons, macrophages, fibroblasts, and cells that may be glial progenitors.⁵⁷ However, the significance of infection of any neural cell is open to debate. For example, Jeffrey and colleagues found BD antigen within the oligodendrocytes of one lamb with the alternative pathology (cerebral cavitation; see later in this section) in which there was no hypomyelination.⁵⁵ Furthermore, BD virus can infect cultured Schwann cells,⁵⁷ but there is no evidence of PNS hypomyelination in this disease.

To explain the failure of central myelin development, an alternative perspective was raised by Barlow and Storey.⁵² They suggested that BD virus could interfere with thyroid function and pointed out that fetal or neonatal thyroidectomy can affect myelin formation, bone growth, and wool development. Anderson and associates⁵⁸ have shown that there is BD viral antigen in the thyroid follicular epithelium and such BD lambs have approximately 30% to 40% lower T3 and T4 levels in their serum. It remains to be established if this is sufficient to account for their hypomyelinogenesis. Similar data on thyroid function have been provided in hypomyelinated kid goats with inherited β -mannosidosis. There have been many investigations of the effects of fetal and postnatal thyroid deficiency because of the occurrence of mental retardation in congenital human hypothyroidism. Both thyroxine- and growth hormone-deficient animals have abnormalities of gliogenesis and reduced CNS myelin.⁵⁹ However, most experimental studies reveal a spectrum of effects of fetal hypothyroidism, including reduced body size, reduced brain mass, reduced brain DNA, as well as some reduction of myelin content.^{60,61} These studies often involve surgical thyroidectomy, which may be performed too late in gestation to severely affect myelin development. In other studies, however, congenital hypothyroidism has been produced by treating pregnant animals with antithyroid drugs,⁶² but the status of CNS myelin has not always been the primary focus of these studies. At this time the hypothyroidism connection in BD hypomyelination remains an appealing hypothesis awaiting conclusive substantiation.

Lambs infected beyond gestational day 80 have progressively milder and less widespread myelin deficits with increasing age at infection. Beyond 80 days or so, the now-immunocompetent fetus responds with the development of

a leptomeningeal and neuroparenchymal polyarteritis; fewer affected blood vessels are found in the visceral tissues. In this presumed Arthus reaction, BD antigen can be demonstrated while the microscopic findings are mainly of adventitial infiltration with macrophages and lymphocytes.^{63,64}

Cases of BD with what Barlow terms the "alternative pathology" have appeared, largely in the course of experimental studies. On rare occasions, BD in twin lambs has been seen, one having the classical and the other the alternative expression of the disorder. In this alternative form of BD, lambs typically are not hypomyelinated but have focal (porencephalic) to extensive (hydranencephalic) cerebral white matter cavitations, sometimes a cystic septum pellucidum, and a small, dysplastic cerebellum.^{65,66} Arthrogryposis has also been seen. What factors precipitate this expression of neural injury is unclear. These destructive lesions are attended by a modest inflammatory reaction, and so the host response may be an important factor, this pattern of cerebral changes perhaps occurring at a time of partial immunity in the fetus.

The state of knowledge of Border disease up to 1981 is reviewed by Barlow and Patterson.⁶⁷

In contrast to the congenital pestivirus infections in sheep (Border disease) and swine (hog cholera), in utero infection with BVD virus much less commonly results in hypomyelination in **cattle**.⁶⁸⁻⁷⁰ In such cases, affected calves are persistently infected at birth, are small, and have tremors that range from mild and subtle to too severe to allow ambulation. Clinically, they may resemble cerebellar disease.⁷¹ Some affected calves die as neonates and, if necropsied, are found to be hypomyelinated and to have abnormal glia reminiscent of those in Border disease. If other affected calves are fed and maintained, their tremor and concurrently their myelin deficit slowly resolve. More commonly bovine fetal BVD infection results in cerebellar degeneration and hypoplasia, retinal dysplasia, cataracts, other ocular defects, and occasionally porencephaly or hydranencephaly. Congenital BVD infection is discussed further in the section on malformations.

A few reports in the older literature record episodes of congenital or neonatal neurological disease in cattle that was of familial and possibly inherited nature. Histopathological findings were commonly mixed, with both hypomyelination and spongy white matter changes. Young reported hypomyelination congenita in **Angus-Shorthorn calves**.⁷² The two female and one male calf studied were unable to stand from the time they were born, and they had a generalized tremor. Postmortem, failure of central myelin development was most marked in the myelencephalon but was also found in the cerebrum, cerebellum, pons, and cervical spinal cord. The pallid white matter was also vacuolated. A congenital ataxia in **Jersey calves**, confined to the progeny of two bulls, was recorded in 1952.⁷³ Pathological changes predominated in the medulla of the cere-

bellum and in folial white matter. Although large areas lacked myelin, the pathological alterations were complex with extensive myelin vacuolation, edema, and failure of development of axons in the white matter and of neurons in some brain stem nuclei (cerebellar nuclei, reticular formation). A disorder of central myelin in **Shorthorn and Hereford calves** was encountered in Canada.⁷⁴ Ataxia was noted within 2 or 3 days of birth. The cerebellomedullary area was affected with a cribriform change in white matter. However, widespread hypomyelination was not described. The disorder in Jersey cattle is also discussed with the spongy degenerations, and, indeed, all three conditions have a spongiform component.

A number of conditions are associated with **hypomyelination in swine**. These disorders have been studied most fully by Bradley and Done in England,⁷⁵ who have subclassified affected piglets as type A and type B. In the former, there are morphological or neurochemical changes to be found in the CNS at necropsy; in type B cases, such changes are lacking, implicating a functional (rather than a structural) disorder to account for the clinical signs. This **congenital tremor syndrome** in piglets⁷⁶ is widely recognized and has been named myoclonia congenita and dancing pig disease. Clinically, the various forms are similar, with affected animals showing rhythmic whole-body tremors that worsen with excitement and cease during sleep. The clinical presentation is very characteristic, with affected piglets bouncing on their digits, hence "dancing" pigs. Spinal cord hypomyelination is a common denominator, but other pathological features vary between the types.

1. **Type A I** is caused by a transplacental infection with wild type or vaccinal hog cholera virus. Animals are susceptible between 10 and 50 days of gestation; earlier infections produce the most severe deficits in the CNS. There is generalized CNS hypomyelination and cerebellar hypoplasia and dysplasia. The spinal cord is hypoplastic. More than 40% of a litter is commonly affected, both males and females, and moderate to high mortalities can be anticipated. Grossly, cerebellar deficits vary from vermian hypoplasia to subtle diffuse hypoplasia that may require cerebellar to whole-brain weights for their demonstration (the cerebellum, transected through the peduncles, should weigh more than 10% of the whole brain mass). Microscopically, there is hypomyelination with widened nodes of Ranvier and irregularities of paranodal loops.⁷⁷ Ultrastructural findings suggested hypomyelination with some phagocytosis of formed and degenerate myelin. The sow is seropositive to hog cholera virus, and the immunity prevents further cases in subsequent pregnancies.
2. **Type A II** is also caused by a transplacental infection, but the agent (presumed to be viral) is unknown. Again, both sexes are affected and usually more than

80% of a litter; however, despite high morbidity, the mortality rate in affected piglets is low, and by 8 weeks tremor is mild. There is normal cerebellar and spinal cord mass but varying degrees of CNS hypomyelination are found.⁷⁸ The CNS total lipids and cerebroside levels are subnormal, and cholesterol esters, characteristic of demyelination, may be found. Infection confers protection for subsequent litters.

3. **Type A III** affects male piglets of Landrace or Landrace-cross breeds and is inherited as a sex-linked trait. The mortality rate is high. Oligodendrocyte numbers are reduced in association with the CNS hypomyelination.⁷⁹ Lipid content in white matter is reduced, and particularly cholesterol, cerebroside, and phospholipid synthesis are diminished.⁸⁰ Ultrastructural examination shows extensive hypomyelination, particularly of smaller-diameter axons, and reduced oligodendrocyte numbers.⁸¹
4. **Type A IV** is inherited in autosomal recessive fashion in Saddleback pigs. Both sexes are affected (approximately 25% of the litter), and the mortality rate is high. Hypomyelination is accompanied by myelin lipid concentrations of approximately 50% of control levels. Cerebroside and phospholipid (plasmalogen) levels are particularly low, and cholesterol esters accumulate, suggesting that myelin formed is unstable and prone to degeneration.⁸² Although fine structural studies⁸³ did not reveal myelin phagocytosis, ballooning and vesiculation of formed myelin were observed, and macrophages contained many fat droplets, presumably neutral lipid from digested myelin lamellae. Oligodendrocyte degeneration was noted, such cells harboring autophagosomes, membranous whorls, and dense bodies. Astrocyte processes with intermediate filaments were conspicuous. Amyelination or hypomyelination affected large- and small-diameter axons.
5. **Type A V** results when pregnant sows are treated with organophosphate antiparasitic compounds between days 45 and 63 of pregnancy.⁸⁴ A congenital tremor develops in approximately 90% of the litter. Treatment at later dates may also produce cerebellar hypoplasia.⁸⁵ Both sexes are susceptible, and many succumb. Pathological findings are cerebellar and spinal cord hypoplasia and some hypomyelination. The cerebellum is small but reasonably proportioned with diminished subpial germinal cells and some Purkinje cell deficiency.
6. **Type B** cases of congenital tremors have not yet shown structural and neurochemical abnormalities. Cause or causes remain to be defined.

The application of neurochemistry as a diagnostic aid in these congenital tremor disorders of swine has been reviewed.⁸⁶

The postnatal development of the canine spinal cord was studied by Fox and colleagues,⁸⁷ whereas Lord and Duncan⁸⁸ have provided extensive and more contemporary information on glial development and myelination. Duncan³¹ has reviewed current knowledge of normal myelination, the pathophysiological and cellular aspects of abnormal myelin development, and the major phenotypes of hypomyelination recognized in the dog. Since 1977, when Greene and associates⁸⁹ described a single male Dalmatian puppy with congenital diffuse body tremors, CNS hypomyelination has been recorded in a number of canine breeds. Affected litters may be reduced by stillbirths and neonatal deaths as well as frank neurological disease. The most extensively studied phenotype is the male **Springer Spaniel dog** (the "shaking pup"). These dogs have a severe generalized tremor from 10 to 12 days of age⁹⁰ that prevents stance or ambulation, and death by 3 or 4 months is common. The tremor is generalized, worsens with stimulation, diminishes with rest, and disappears during sleep. A spontaneous, pendular nystagmus may be observed. The disorder is transmitted as an X-linked trait, and some heterozygous carrier females may manifest a mild, transitory tremor in the first month of life. At necropsy of affected male puppies, the central white matter is dull and gelatinous compared with peripheral myelin. Microscopically, many axons are unmyelinated or hypomyelinated, more so in the brain than the spinal cord. Myelin formed is thin, poorly compacted with shortened internodal length.⁹¹ Arrangement of the paranodal lateral loops is frequently abnormal, and astrocytic processes may be found insinuated between the axon and its myelin sheath. Oligodendrocyte numbers are diminished, and those identified have dilated cisternae (perinuclear and granular endoplasmic reticulum) harboring flocculent material (myelin protein?).⁹² Analysis of myelin from affected pups shows severe reduction of myelin proteolipid protein with a proportionately greater expression of the related DM-20 protein⁹³ and lesser quantities of other myelin proteins such as basic protein.⁹⁴ The little myelin formed has the biochemical hallmarks of immaturity. In female heterozygotes, myelin mosaicism has been observed with nonmyelinated or hypomyelinated plaques interspersed among normally myelinated tissue.⁹⁵ This effect is thought to reflect the random inactivation of one X chromosome in carrier females.

The 5-week-old male **Samoyed** that we described⁹⁶ was clinically and neuropathologically similar to the Springer Spaniels. In previous breedings, neonatal tremors and death had approached 40% of the litters of Samoyed puppies. Grossly the white matter in the brain was very pale, and routine stains revealed a profound failure of myelin development (Fig. 5-58). Myelin basic protein immunocytochemistry identified occasional, thinly myelinated CNS axons and normal dense staining of peripheral myelin. Oligodendrocytes were remarkably depleted in number,



Fig. 5-58. Hypomyelination, dog. **A**, Spinal cord. Normal myelination of spinal roots. (Luxol fast blue, cresyl echt violet, $\times 140$.) **B**, Electron microscopy of spinal cord funiculus reveals unmyelinated axons (*a*) in an astrogliotic background. A few poorly compacted myelin lamellae are seen about a couple of axons (*arrows*). ($\times 12,500$.)

compared to age- and site-matched control canine tissue; those identified were light or medium types, suggesting retarded glial differentiation. There was a relative astrogliosis and a remarkable increase in microglial cells, the significance of which is open to conjecture. The presence of these cells may indicate oligodendroglial necrosis (Blake-more, personal communication 1987) some of which occurs normally during active myelination.

A congenital tremor syndrome associated with abnormal central myelination occurs in **Chow dogs**.⁹⁷ Both males and females are affected from about 2 weeks of age. They stand with the pelvic limbs basewide and have a rocking horse motion when attempting to ambulate. All limbs are hypermetric. From three litters, five affected dogs were seen; three survived, and their condition plateaued at 6 to 8 months, then slowly improved to normality at 1 year of age. Pathological examinations were made of one 4-week-old and one 3-month-old Chow, and biopsies were available from two others. The important findings were widespread lack of myelin development with a few tracts (cerebellar peduncles, spinal fasciculus proprius) well myelinated. Ultrastructurally, axons were found to be thinly myelinated or nonmyelinated amid a dense fibrous astrogliosis. Gliofibrillary oligodendrocytes (a cell considered by some to be a glial cell progenitor) were observed; these are oligodendrocytes with cytoplasmic filament bundles typical of astrocytes. This is a novel finding that suggests an aberration in normal gliogenesis. Such cells have also been encountered in human

mixed gliomas. Clinical improvement noted with age could reflect compensation or further myelination. Studies of two older Chow Chows (15 months and 3 years)⁹⁸ showed improved myelination in the brain with some persisting hypomyelination in the lateral and ventral spinal cord funiculi. Some abnormal myelin arrangements were encountered, such as redundant loops that produced irregular, excessively thick sheaths.

Hypomyelination in **Weimaraner dogs** was reported in the United States.⁹⁹ Generalized body tremors and dysmetria affected pups of both sexes at 1 to 3 weeks of age. Some affected pups slowly improved but not so the most severe cases. Pathological findings are typical of this group of disorders, with widespread hypomyelination, particularly conspicuous in the subpial areas of the lateral and ventral spinal funiculi. Oligodendrocyte numbers are reduced. Ultrastructurally, there are thin, poorly compacted sheaths, many nonmyelinated fibers, and a few relatively normally myelinated, smaller-caliber fibers. In the United Kingdom, a 7-week-old female Weimaraner puppy presented with pelvic limb ataxia and weakness.¹⁰⁰ When moving quickly, it had a bunny-hopping gait. The puppy was euthanized and found to have spinal subpial myelin pallor similar to the previous cases but involving all three funiculi. Affected white matter was vacuolated and gliotic, and the pia-arachnoid was thickened. Further changes were severe vacuolation within the dorsal horns, lateral cuneate nucleus, and reticular formation. Axonal spheroids were found in the

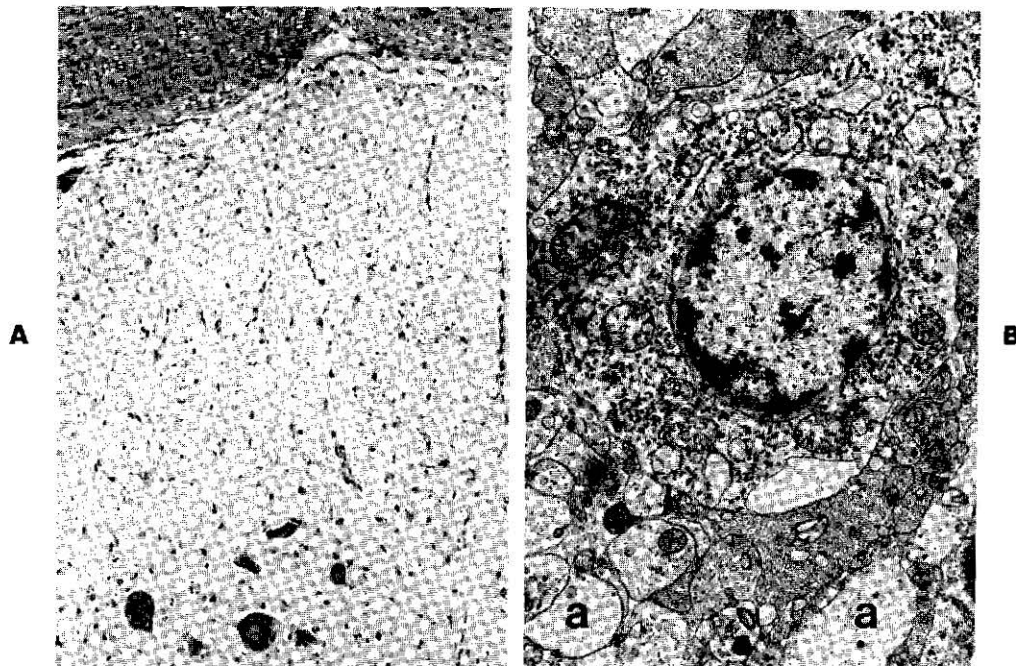


Fig. 5-59. Hypomyelination, cat. **A**, Staining of PNS myelin in the spinal root contrasts with the spinal cord. (Luxol fast blue, cresyl echt violet, $\times 140$.) **B**, Electron microscopy of cervical spinal cord funiculus shows a light oligodendrocyte with dilated cisternae of rough endoplasmic reticulum. Axons (*a*) are unmyelinated amid astroglial processes. ($\times 12,500$.)

cerebellar granule cell layer and internal capsule. The relationship of these two syndromes in Weimaraners remains to be clarified. Two male crossbred **Lurcher** puppies developed generalized continuous tremors from 2 weeks of age;¹⁰¹ one pup improved and by 16 weeks had fully recovered. The other remained static and at 8 weeks was sacrificed. It showed myelin pallor with some tracts apparently more densely myelinated. By electron microscopic examination, many axons were found to be thinly myelinated, and sheath thickness was irregular in the larger-diameter axons. Glial cells were normal, and the PNS was unaffected. A hypomyelinating disorder has been recorded in **Bernese Mountain dogs**.¹⁰² Tremors began at 2 to 2.5 weeks of age in both male and female puppies, and an autosomal recessive mode of inheritance was proposed. Some affected animals survived to adulthood with variably severe residual tremor, exacerbated by stress or excitement. Studies of affected puppies at 9 weeks of age reveal thinly myelinated axons with shortened internodes. A small proportion of the oligodendroglia had cytoplasmic abnormalities with dilated cisternae, membranous whorls, and osmiophilic deposits. Data from breeders indicate an onset of the disorder between 2 and 9 weeks of age, and sometimes even later. Finally, we can return to the case report of the male **Dalmatian pup** with rhythmical, generalized, whole-body tremors since birth.⁸⁹ This pup was markedly hypomyelinated with oligodendrocyte degeneration and diminished oligodendrocyte numbers. There is also a 1958 report

on a hypomyelinated (leukodystrophic) Spaniel dog (see paper number 31 for reference).

Given the number of syndromes now recognized in the dog, the absence of comparable cases of **hypomyelino-genesis congenita in the cat** is perhaps surprising. We have encountered two cases in littermate Siamese kittens (one female, one in which the sex was not recorded) that acutely developed tremors and frenzied behavior at 4 weeks of age.¹⁰³ Pathological studies at 6 weeks revealed neuraxial hypomyelination, most striking in the lateral and ventral spinal cord funiculi (Fig. 5-59). There was modest astrogliosis in affected white matter and diminished staining for MBP. Ultrastructural examination showed a predominance of amyelinated axons, with a minority having thin, poorly compacted sheaths.

Since perhaps the 1950s, a number of spontaneous mutations in laboratory **mice** and **rats**, which have resulted in a variety of patterns of CNS hypomyelination, have been recognized. These mutant animals, identified by the presence of tremors that begin soon after birth, have been expanded into colonies and extensively studied around the world. They provide a unique opportunity to investigate myelinogenesis, for each mutant represents a disorder in a specific gene important in production of the myelin sheath. Phenotypically similar disorders are seen in domestic animals, but in these laboratory animals there are distinct advantages possible, including the breeding of double mutants¹⁰⁴ and the reconstitution of defective genotypes by

transgenic techniques. The molecular biology of myelin proteins and the abnormalities in these mutants have been reviewed.^{105,106}

The **shiverer mouse** acquires a generalized tremor beginning at about day 14 of life and subsequently develops seizures of increasing frequency. Affected mice succumb between 90 and 150 days of age.¹⁰⁷ There is CNS hypomyelination, resulting from a mutation of the MBP gene on chromosome 18. Northern blots show that shiverer brain lacks the mRNA for MBP. Ultrastructurally, any myelin formed is tightly compacted at the intraperiod line, but there is a deficit in the compaction of oligodendrocyte cytoplasm to form major dense lines, the membrane site of MBP. Myelin basic protein constitutes part of PNS myelin also, but peripheral myelin is only mildly changed. The introduction of the wild-type MBP gene into the germ line of the shiverer mouse largely corrected the phenotypic disorder.¹⁰⁷ Murine MBP consists of at least four species (molecular weights 14 to 21.5 kDa), and transgenic shiverers, which produce the smallest component (14 kDa), are substantially improved.¹⁰⁸ In the shiverer *mld* mutant, the MBP gene is duplicated, which produces a phenotype like shiverer but milder.

The **jimpy mouse** mutation is a recessively inherited, sex-linked CNS disorder. Tremors in affected hemizygous male mice begin on about postnatal day 11; because of their progressive intensity, the mouse's lifespan is only 25 to 30 days. At postmortem examination, there is a profound deficiency of central myelin apart from small patches of poorly compacted membranes lacking intraperiod lines. The mutation affects the proteolipid protein (PLP) gene on the X chromosome, and there is a virtual absence of CNS PLP synthesis. As is seen in other X-linked dysmyelinating disorders, oligodendrocyte necrosis, resulting in a paucity of these cells, is conspicuous. The disorder is highly comparable to the human X-linked Pelizaeus-Merzbacher syndrome (see previously), which has been associated with PLP gene mutations,^{109,110} and to the myelin-deficient rat,¹¹¹ the Springer Spaniel, and the type A III pig. The absence of PLP gene expression seems to have lethal consequences for oligodendrocytes, suggesting that its role may extend beyond providing approximately 50% of the protein component of central myelin, perhaps to aspects of glial differentiation. The recently described **Rumpshaker mouse** is a nonlethal, X-linked mutation.¹¹² Tremors begin at about day 12 of life but do not progress to seizures, and affected mice are viable and can be bred. If necropsied, there is central hypomyelination with normal PNS myelin. Although PLP expression is virtually lacking, oligodendrocyte numbers are not reduced and actually are greater than in wild-type mice. Rumpshaker is an allele of jimpy with hypomyelination, but with oligodendrocyte survival, suggesting at least two functions for the PLP gene products.¹¹³

The **myelin-deficient mouse** is an autosomal recessive trait producing caudal trunk and hindquarter tremors from

about day 12 of life. Seizures begin at about 1 to 2 months of age and the life expectancy is 5 to 9 months.^{114,115} Affected mice have severe CNS hypomyelination with normal peripheral nerves. Many central axons are unmyelinated; a minority have narrow sheaths that are abnormally formed and lacking a major dense line. White matter is deficient in MBP, but other myelin proteins are present. In myelin-deficient mice, the MBP gene has a mutation affecting post-transcriptional regulation,¹¹⁶ resulting in its expression at low levels and in a delayed pattern. The **quaking mouse** is a novel mutant in that aberrations of myelin development affect both oligodendrocyte and Schwann cell compartments. This nonlethal disorder has been mapped to chromosome 17 and is a recessive trait. The underlying defect has not been elucidated; myelin components are present but in markedly reduced quantities.¹¹⁷ In the PNS, failure of normal compact myelin formation seems to be associated with abnormalities in mobilization of myelin-associated glycoprotein.¹¹⁸

Severe central hypomyelination is seen in the **myelin-deficient rat**, a mutant of the Wistar rat strain. Affected males in this X-linked disorder can be identified by their tremor, which begins at 12 to 14 days of age. A week or so later, this is followed by progressively worsening generalized seizures such that the life expectancy is only of the order of 4 weeks. Reducing the seizure activity prolongs their lives. Affected rat pups are severely deficient in myelin,¹¹⁹ but a few ensheathed axons are found in the spinal cord. Any myelin formed is of reduced periodicity due to abnormal condensation of the intraperiod line. This is the site where PLP is normally found, and its absence is thought to account for the intraperiod line abnormality.¹²⁰ As in other X-linked PLP disorders, oligodendrocyte numbers are diminished. The mutation in myelin-deficient rat PLP gene, a single nucleotide difference from normal rat PLP, has been identified.¹²¹ Myelin of the PNS is unaffected. Neurological disorder in the tremoring **zitter rat** is inherited as an autosomal recessive trait and is associated with two morphological abnormalities. Spongy degeneration appears by 3 weeks of age in the gray matter of the pons and thalamus and becomes more widespread with advancing age. There is also CNS hypomyelination, associated with oligodendrocyte and myelin sheath abnormalities.¹²²

The mutant black **Syrian hamster** develops tremors at about 2 weeks of age. The animals' life span and sexual maturity are unaffected, but some tremor persists for life. The disorder is an inherited autosomal recessive condition. The CNS has diffuse, marked hypomyelination, while the PNS is unaffected. Glial cell numbers are comparable to control animals, but ultrastructural studies show incomplete myelination with a marked reduction in myelin sheath thickness.¹²³ The **myelin-deficient CBB hamster** develops a tremor at approximately 2 weeks of age. The disorder is not lethal, and tremors disappear at around 100 days.¹²⁴ Central myelination is severely deficient, particularly of small-cal-

iber axons. However, myelination is slowly progressive with advancing age, and that formed is relatively normal. The mutation is transmitted as an autosomal, recessive trait.

Finally a number of nutritional and toxicological studies have pointed to effects on central myelination. Postnatal nutritional insufficiency in neonatal rats stunted body growth, brain weights, and myelin lipid concentrations.¹²⁵ Vitamin B₁₂ deficiency in newborn children is associated with hypomyelination, although other effects on the CNS are anticipated.¹²⁶ Treatment of embryonated hens' eggs with 2,4-D (2,4-dichlorophenoxyacetic butyl ester) diminished CNS myelin by 65%;¹²⁷ postnatal exposure to inorganic lead, triethyl tin, or tellurium in rats can produce CNS myelin deficits.^{128,129}

Spongy degeneration

Under the rather nondescript heading of **spongy degeneration**, we draw together a series of progressive, invariably lethal neurological diseases of animals and humans in this section. The basis for their comparison is mainly pathological, although they share considerable clinical homology. These conditions are primarily (but not exclusively) leukoencephalopathies and may be hereditary. From the outset, they must be clearly separated from the novel, transmissible spongiform encephalopathies such as scrapie of sheep and goats and the human Creutzfeldt-Jakob disease. The latter diseases are acquired and their cytopathology is focused within the perikaryon and processes of the neuron.

The best-characterized member of this group is the spongy degeneration of the brain in children, first reported by van Bogaert and Bertrand in 1949. Canavan made early contributions also, and thus, in an attempt to achieve some specificity, this syndrome is often described as **spongy degeneration of van Bogaert-Bertrand type** or as **Canavan's disease**. Three patterns are recognized in children: congenital, infantile, and juvenile forms. The infantile form is most common and frequently afflicts Jewish children at about 6 months of age. They show megalencephaly, mental retardation, and hypotonia, which progresses to spasticity and seizures. The congenital form is similar, with onset at or soon after birth. A rare juvenile form occurs in children beyond 5 years, shows no predilection for Jews, and has cerebellar signs.

At autopsy of these infants, the brain is usually heavy, the lateral ventricles dilated, and the white matter grayish and gelatinous. Microscopically, the white matter is diffusely vacuolated, a change described as "status spongiosis," and also it is pallid, an impression confirmed with myelin stains. Spongy change extends from white matter into the margins of the gray matter and is accompanied by the formation of Alzheimer type II astrocytes; oligodendrocytes are normal. Ultrastructurally, the spongiosis is found to result from splitting and ballooning of myelin sheaths and from the swelling of astrocytes, which have watery cytoplasm. Structural abnormalities of the mitochondria within astrocytes

have been considered to be significant; these mitochondria are strangely elongated, have a filamentous core occasionally bearing focal densities,¹³⁰ and have abnormally arranged cristae.¹³¹ Astrocytes are important in the homeostasis of fluid and ion transport within the neuroparenchyma, and energy deprivation could lead to abnormal fluid accumulation. It has been proposed that an astrocytic mitochondrial defect in adenosine triphosphatase (ATPase) activity may underlie the pathological process, although evidence for ATPase deficiency has not been universal.¹³⁰ Recent biochemical investigations of children with this spongy degeneration have detected elevated levels of N-acetylaspartic acid in blood and urine and depressed levels of tissue aspartoacylase activity,¹³²⁻¹³⁴ which may be the underlying defect. It is interesting that van Bogaert-Bertrand spongy degeneration of humans is often viewed as a leukodystrophy, whereas in animals, whether rightly or wrongly, comparable syndromes have not so been categorized.

With this prelude, we shall now review pathologically comparable syndromes in animals.

Spongy degeneration in white matter

In **dogs**, spongy degeneration was described in two female littermate **Labrador Retrievers**.¹³⁵ The parents of the litter shared a common sire, an important point as inbreeding is a frequent feature of these syndromes where they appear in animals. These two Labradors showed a progressive neurological disorder, distinguished by extensor rigidity of limbs, opisthotonic posturing, and cerebellar ataxia. Deficits began at 4 and 6 months of age and worsened over the next few months. The episodes of extensor rigidity were exacerbated by excitement and probably represent tetanic spasms rather than true seizures. At necropsy of both animals, the brain was grossly unremarkable, apart from a yellowish area in the cerebellar medulla in one dog. Microscopically, the white matter was diffusely vacuolated and poorly stained.¹³⁶ Hypertrophic astrocytes with abundant eosinophilic cytoplasm were prominent; some showed degenerative changes and were granular and shrunken. Axons showed only occasional focal swellings. Retinal degeneration was observed in one dog. Electron microscopic examination showed pronounced myelin vesiculation and intramyelinic splitting (at the intraperiod line), leading to vacuole formation. Rupture of vacuoles resulted in the formation of large multilocular structures. Swollen astrocytes had watery cytoplasm, somewhat diluted of organelles and contained abnormal mitochondria. Cristae were poorly preserved, focal densities were observed, and many harbored paracrystalline inclusions. That these mitochondrial changes are the same as those observed in children with spongy degeneration is uncertain; the canine tissue had been formalin-fixed and mitochondria are prone to artifactual disruption. The striking paracrystalline inclusions somewhat resemble those observed within mitochondria in equine cells.^{137,138} A primary membrane-associated metabolic defect is proposed, result-

ing in altered fluid and ion homeostasis affecting both astrocytes and compact myelin.¹³⁶

Spongiform degeneration of white matter was described in a **Samoyed pup**;¹³⁹ four of a litter of nine developed generalized tremors. Necropsy of one, at 18 days of age, revealed diffuse white matter vacuolation. Electron microscopic examination showed splitting and vacuolation of myelin sheaths. Astrocytes were unaffected.

In the **Silkie Terrier dog**, a congenital tremor syndrome was observed in three of a litter of five puppies.¹⁴⁰ Repetitive muscular contractions were severe, producing a bouncing, almost dancing type of action. Histopathological examination of one dog at 5 weeks revealed poorly stained white matter and diffuse vacuolation. The cerebral cortex and spongiform white matter contained Alzheimer type II astrocytes, identified by their swollen, vesicular nuclei.

Spongiform degeneration in the **Egyptian Mau cat** is reported by Kelly and Gaskell;¹⁴¹ significantly, the Egyptian Mau line is inbred. Two 7-week-old female littermate kittens, noticed to be small for their age, had pelvic limb ataxia with hypermetria. These neurological signs worsened, with episodic depression, inactivity, and seizures. One kitten was sacrificed at 4 months and showed extensive vacuolation of the brain, affecting both gray and white matter, more so the latter. No abnormal glia were observed, and axons were normal. Ultrastructurally, the vacuoles were intramyelinic because of splitting at the intraperiod line. There was no evidence of active myelin breakdown.

Spongy degeneration has been associated with a neurological disorder of **silver foxes** in Norway.¹⁴² Preliminary breeding studies suggest that this disease is inherited as an autosomal recessive trait. The clinical presentation is of pelvic limb paresis and ataxia between 2.5 and 4 months of age. After 4 to 8 weeks, the clinical signs are non-progressive, and affected animals have shown clinical improvement. Neuropathological studies showed that throughout the neuraxis the white matter is markedly vacuolated and deficient in myelin. Ultrastructural examination revealed intramyelinic vacuoles with opening of the sheath at the intraperiod line, demyelination, and, in some instances, the unusual observation of partial axonal demyelination, oligodendrocyte vacuolation, and some degree of remyelination in chronically affected animals.¹⁴³

Spongiform degeneration in **cattle** occurs with some frequency in the Hereford breed. Perhaps most similar to van Bogaert-Bertrand type is the disorder designated **congenital cerebral edema** by Jolly in New Zealand,¹⁴⁴ affecting inbred horned Hereford cattle. From birth, affected calves (of both sexes) are unable to stand and lie in lateral or sternal recumbency. They show coarse tonic muscular contractions that diminish during sleep and are amplified by physical stimulation. In Jolly's study, seven of nine affected calves had abnormal nystagmus. At necropsy, the brains appeared wet and showed mild internal hydrocephalus. Pronounced status spongiosis of gray and white matter was found on microscopic examination. Sponginess in the gray matter.

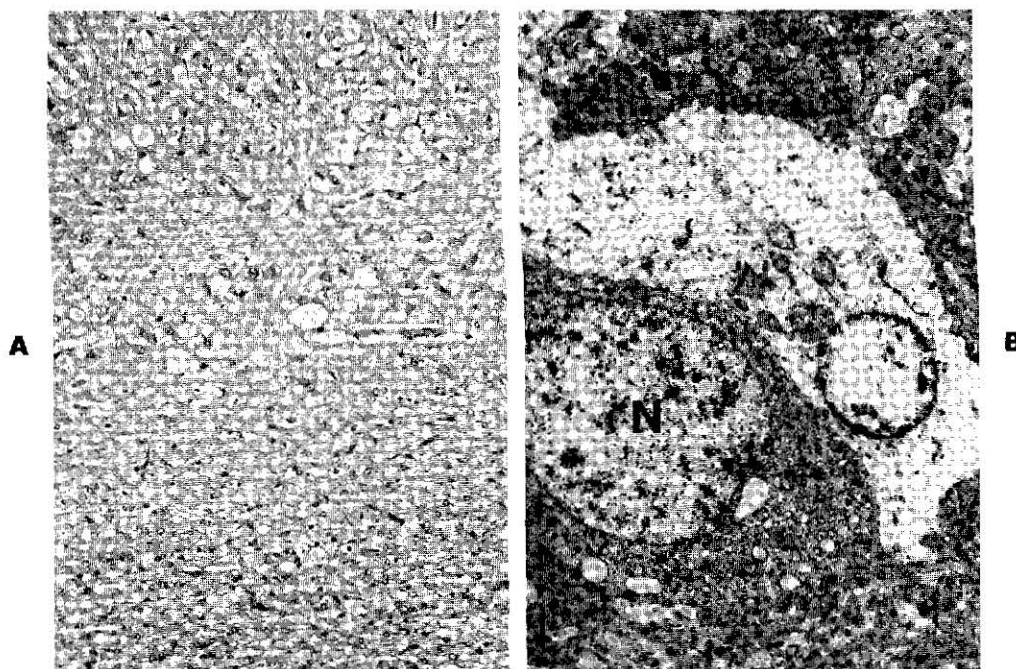


Fig. 5-60. Cerebral edema, calf. **A**, Spongy change in the cerebral cortex and subcortical white matter. (H&E, $\times 140$.) **B**, Ultrastructural detail of the cerebral cortex. A very distended, watery satellite astrocyte abuts its neuron (nucleus, N). ($\times 3600$.)

prominent in the cerebral and cerebellar cortices and the basal nuclei, resulted from astrocyte swelling (Fig. 5-60). This produced a spongy appearance around neurons, their satellite cells, and where astrocytic end feet abut capillaries, which contrasted with the otherwise compact neuropil. Alzheimer type II astrocytes were not present. White matter was pallid, diffusely spongy, and severely myelin deficient; axons were intact. Oligodendrocyte somata were unusually prominent. Evidence of mild myelin degeneration was afforded by Marchi-positive material and, in frozen sections, neutral lipid. The designation cerebral edema was justified by the demonstration of elevated water content in the brain of an affected calf. Ultrastructurally, hydropic change in protoplasmic astrocytes was dramatic, producing swollen, watery cells sometimes with distended endoplasmic reticulum. White matter sponginess was found to result from an expansion of extracellular spaces (presumably astrocytic swelling) and from splitting and ballooning of myelin lamellae. Occasionally oligodendrocytes showed hydropic changes also. Many axons were unmyelinated or possessed only very thin sheaths, yet evidence of myelin degradation was mild, suggesting a concurrent hypomyelination. We have studied one case ultrastructurally and also gained the predominant impression of hypomyelination, rather than of demyelination of normally formed sheaths. Breeding records for all affected calves were lacking, but inbreeding was clear, and an autosomal recessive mode of inheritance proposed.

In 1969, five years before Jolly's report, Cordy and his colleagues described a novel, inherited neurological disorder in male and female Hereford calves.¹⁴⁵ Cases of this new condition, which they called **hereditary neuraxial edema**, occurred in the polled Hereford breed (and possibly also in horned Hereford calves) in a pattern compatible with an autosomal recessive mode of inheritance. Breeding experiments with polled Herefords in Australia have substantiated this proposal.¹⁴⁶ Unable to rise from birth, affected calves lie in lateral recumbency but are bright and alert and suckle a bottle that is offered. Characteristically, these calves are dramatically hypersensitive to stimulation by touch or sound, either stimulus inciting a tetanic extensor spasm of the limbs and body (without opisthotonus) which lasts for a few seconds. If affected calves are held and supported in a normal standing posture, they enter a more prolonged spasm that produces a stiff, saw horse-like posture and, commonly, apnea.

Three calves in Cordy's report died of intercurrent pneumonia and enteritis; the others were euthanized within a week of birth. Apart from the pneumonia and enteritis, gross postmortem examination was unremarkable except for bilateral proximal femoral fractures in one calf. Interestingly, coxofemoral joint trauma has been found to be a hallmark of this syndrome.^{146,147} The brains of many calves studied were grossly normal, but some were swollen with flattened gyri. Microscopically, there was a variably severe spongy

vacuolar change of the terminal portions of white matter tracts and of some gray matter areas. Spongiform change particularly involved the reticular formation, cerebellar nuclei and folia, nuclei in the pons and medulla, basal nuclei and corona radiata, and deep cortex of the cerebrum. These changes were mild (6 of 12), moderate (3 of 12), and severe (3 of 12). Axons were largely normal, save for a few fusiform swellings. Alzheimer type II astrocytes were lacking and the vacuolar change did not incite a histiocytic response. To their considerable credit, Cordy and his colleagues considered this to be a metabolic disorder with the vacuolation, which they interpreted as edema, a secondary development. One human disease, which they felt that this calf disorder resembled, was maple syrup urine disease, an inherited disorder of branched-chain ketoacid metabolism. Happily, the admirable studies by Harper and Healy in Australia have clarified the picture. These workers have found that there are two, distinct, neurological syndromes affecting neonatal Hereford calves within the umbrella of neuraxial edema. One, clinically evident from the time of birth, is marked by both spontaneous and stimulus-responsive extensor spasms, femoral and/or acetabular fractures, or just cartilaginous erosions (probably beginning in utero) and a lack of significant CNS changes. Affected calves have a gestational period of approximately 274 days, compared with 284 for unaffected calves; consequently, affected calves are amongst the first of a new calf crop.¹⁴⁷ Spasms have been observed in calves within 2 minutes of birth and may be induced by normal maternal licking by the dam.¹⁴⁶ This condition has been named **inherited congenital myoclonus** of polled Hereford calves.¹⁴⁸ Blood and Gay¹⁴⁹ report their experience with 9 cases in polled Hereford calves in Australia, in which examination of the CNS was uniformly negative. In the absence of morphological changes, a functional failure of inhibitory feedback to interneurons at the spinal cord level has been proposed to explain the clinical signs. This hypothesis is supported by the demonstration of a severe reduction in tritiated-strychnine binding sites in spinal cord membranes, reflecting a deficiency of, or defect in, the inhibitory glycine receptors that are blocked by strychnine.¹⁵⁰

The second syndrome is evident within the first few days of life, but not necessarily from birth. These calves, sometimes briefly walking and suckling normally, soon become dull, recumbent, and opisthotonic.^{151,152} Tremors and tetanic spasms are seen in a minority. At necropsy, they have the spongiform changes in white (Fig. 5-61) and gray matter, particularly in mixed areas such as the brain stem, as described by Cordy and colleagues in 1969.¹⁴⁵ Electron microscopic examination reveals the basis for the spongiform change, namely, intramyelinic vacuole formation, mostly involving outer myelin lamellae.¹⁵³ Oligodendrocytes show mild degenerative changes. The urine has a burned-sugar odor, and chromatographic analysis of urine, serum, or CSF reveals elevated concentrations of branched-chain amino

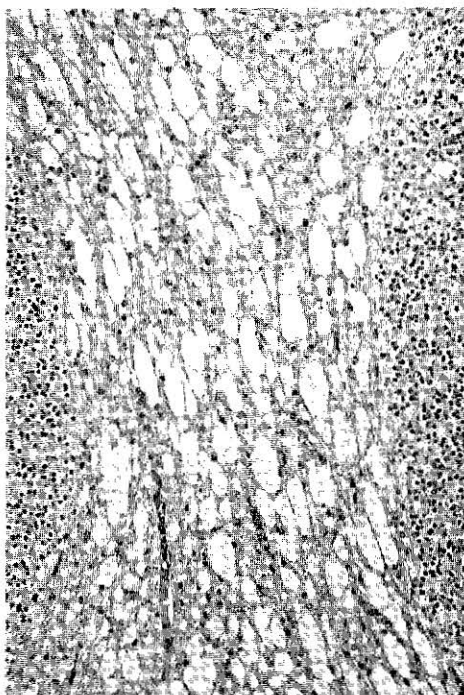


Fig. 5-61. Maple syrup urine disease. Vacuolation of myelin sheaths, cerebellum. (H&E, $\times 140$.)

acids (valine, leucine, and isoleucine), consistent with a **branched-chain ketoacid decarboxylase deficiency**.¹⁵¹ Because of the odor imparted to the urine, this syndrome is known as **maple syrup urine disease** (MSUD) and in children results in lethargy and seizures soon after birth. This is the first of the aminoacidurias described in animals and should encourage similar biochemical studies of other idiopathic, familial neurological disorders. In humans, other inherited disorders of amino acid metabolism with which encephalopathy is associated include phenylketonuria, homocystinuria, and hyperglycinemia.¹⁵⁴ In Canada, MSUD has been reported in polled and horned Hereford cattle,¹⁵⁵ and doubtless further reports will follow.

Distinguishing features of congenital tetany/myoclonus and MSUD of Hereford calves are provided in Table 5-1.

Duffell has reported on a neuraxial edema in Hereford calves in the United Kingdom.¹⁵⁷ All calves were unable to stand at birth and exhibited a tremor and hyperesthesia with intermittent extensor spasms, and some also had abnormal nystagmus. Of eleven Hereford calves studied, nine had extensive CNS vacuolation in both gray and white matter areas, also accompanied by hypomyelination, and so most closely resemble the cerebral edema of horned Herefords described by Jolly.¹⁴⁴ Paradoxically perhaps, these nine English Herefords were polled. However, polled Herefords are derived from horned Hereford cattle, and so the same syndromes may be seen in either line. Duffell's cases 1 and 2 were not hypomyelinated and, although horned,

Table 5-1. Congenital tetany and MSUD in Hereford cattle

| | Congenital tetany | MSUD |
|-------------------------|--|---|
| Breeds | Polled Hereford Polled Hereford cross | Polled Hereford Horned Hereford Possibly others |
| Inheritance | Autosomal recessive | Probably autosomal recessive |
| Onset of clinical signs | Prior to birth | From birth or within the first week of life |
| Characteristic signs | Tetanic spasms in response to touch or sound | Dullness and opisthotonus |
| Urine | Normal | Aroma of burned sugar |
| Pathology | | |
| Joints | Traumatic injury to coxofemoral joints | Joints normal |
| CNS | Normal | Status spongiosis |

From Healy PJ, Harper PAW, Dennis JA: Diagnosis of neuraxial oedema in calves, *Aust Vet J* 63:95-96, 1986.

may be examples of MSUD; material to confirm this (by chromatographic analysis) was not available.¹⁵⁸ In summary, in the Hereford breed, the following syndromes, defined by their distinguishing pathological features are:

1. Inherited congenital tetany—no CNS lesions
2. Maple syrup urine disease—CNS white matter and some gray matter spongiosis; elevated levels of branched-chain amino acids in tissues and body fluids
3. Cerebral edema—CNS gray and white matter spongiosis and hypomyelination
4. Congenital hypomyelination of Herefords—CNS gray and white matter spongiosis and hypomyelination

Conditions three (New Zealand) and four (United Kingdom) may be the same.

In 1962, Fankhauser¹⁵⁹ recorded his experience with a syndrome of **cerebral edema in Swiss Simmental cattle**. Most were affected when between 1 and 2.5 years of age and presented as single cases within a herd. Approximately 50% were in poor condition and had become stunted weeks to months prior to the onset of acute neurological disease. Affected cattle appeared nervous and were hyperactive and restless; many were blind with normal ocular reflexes. The gait was staggering, and cattle that became recumbent could not regain their feet. The CSF was unchanged. At necropsy, the brain was grossly edematous in many cases. Microscopically, a vacuolar edematous change affected the brain parenchyma, mainly white matter; the lesion is reminiscent of hepatic (or renal) encephalopathy in cattle (Fig. 5-62). Inflammatory changes and gliosis were lacking.

In 1952, Saunders and others described a neurological

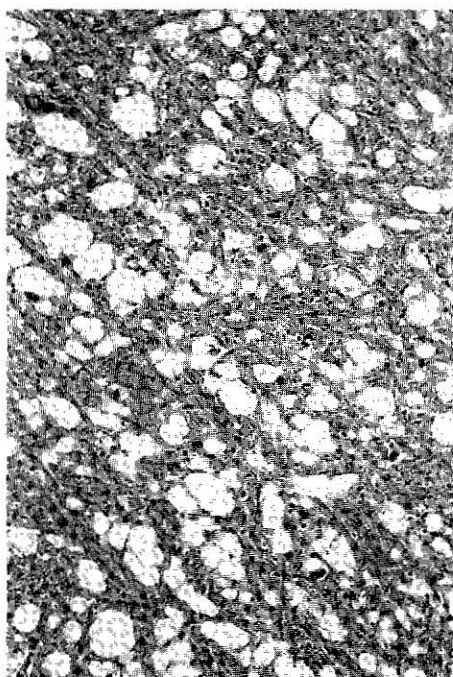


Fig. 5-62. Cerebral edema, Swiss cattle. Spongy change in thalamus. (H&E, $\times 140$.)

disorder that affected **Jersey calves** either at or within a couple of weeks of birth.¹⁶⁰ Clinical signs were of cerebellar ataxia, and animals studied postmortem had a marked pallor and edematous, spongy loosening of the white matter of the cerebellar medulla, white matter cores of cerebellar folia, and the brain stem. Some nuclei were depleted of neurons, particularly in the reticular formation and cerebellar medulla. An autosomal recessive mode of inheritance of this disorder was proposed, and its occurrence ceased when two bulls were removed from the herd. Whether this condition was a metabolic encephalopathy or even a myelin aplasia was not established; it was mentioned previously with the hypomyelinating conditions.

Hartley and Loomis¹⁶¹ briefly recorded a sporadically occurring **spongiform encephalopathy of mature sheep** in Australia. Named Murrurundi disease for the district in which it has been recognized since 1929, it presents as progressive pelvic limb ataxia in 2- to 5-year-old sheep. Neuropathological study reveals a disseminated leukoencephalopathy, most severe in the thalamus, pons, and medulla. Two of four sheep studied also showed vacuolation of neuronal cell bodies in the medulla; further, three had a mild, nonsuppurative encephalomyelitis. Some evidence of focal axonal swelling was also found, and it has been suggested that this disorder is the same as ovine segmental axonopathy (see the section on neuroaxonal dystrophy).

In the laboratory species, spongy degeneration has been described in outbred **Swiss-Webster mice**.¹⁶² From early life, affected animals could be identified by their failure to thrive, cranial enlargement, and a spontaneous tremor. Star-

ting from sleep would evoke an extended, rigid posture, reminiscent of inherited congenital tetany/myoclonus of Hereford calves. At necropsy, the brains were soft with mild enlargement of the lateral ventricle. Microscopic examination revealed a dramatic status spongiosis, diffusely involving white matter and spilling into the gray; changes were progressive with advancing age. Ultrastructural changes were ascribed to astrocytic swelling, while myelin sheaths were thought to be unaffected. In **rats** older than 24 months of age, a vacuolar or spongiform encephalopathy has been observed, affecting the cerebrum, midbrain, and cerebellum. Either white matter or both gray and white matter may be affected.¹⁶³ In **hereditary ataxia of rabbits**,¹⁶⁴ splitting of myelin sheaths and a ballooning degeneration is observed. However, lesions are scattered primarily in gray matter areas of the brain stem and their associated tracts, particularly the vestibular, cochlear, and cerebellar nuclei.¹⁶⁵

Spongy degeneration in gray matter

Finally, there are a few syndromes of spongiform degeneration distinguished by their involvement of gray matter. In a family of **Bull Mastiff puppies**, a neurological disorder affecting both sexes has been noted, usually between 4 and 7 weeks of age.¹⁶⁶ Clinical signs reflect a diffuse CNS disorder and include ataxia with proprioceptive deficits and hypermetria, head tremors, visual deficits, a propulsive gait, dullness, and sometimes bizarre behavior. Postmortem studies of six affected pups revealed dilation of all ventricles and the aqueduct. Microscopically, there was an encephalopathy reflected by severe, bilaterally symmetrical vacuolation and gliosis, which was most conspicuous in the cerebellar nuclei. The caudal colliculi and lateral vestibular nuclei were more mildly affected. The spongiotic neuropil contained spheroids, whereas neuronal cell bodies seemed unaffected. The basis for this vacuolar change—myelin swelling? glial swelling?—and the underlying biochemical derangement remain to be clarified. Pathologically, a somewhat similar syndrome has been observed in **Saluki puppies** in Canada and the United States. Clinical signs have appeared at approximately 2 to 3 months of age and have included some or all of the following: aimless running, circling, and doing back flips. Affected puppies appear to sleep very deeply and excessively; they may cry loudly within a few seconds of waking. Pathological changes predominate in gray matter, particularly the neuropil of nuclei such as the olives and the cerebellar nuclei (Fig. 5-63); there is a pronounced spongiosis, accompanied by swelling of astroglial nuclei. The lesions extend somewhat into white matter, for example at the junction of the lentiform nucleus with the internal capsule. This spongiform degeneration is found also in the deep laminae of the cerebral cortex, the thalamus, pontine tegmentum, and nuclei of the medulla oblongata.¹⁶⁷ In one litter, mild lesions were found in two clinically normal pups.

Carmichael and associates¹⁶⁶ suggested that a genetic dis-

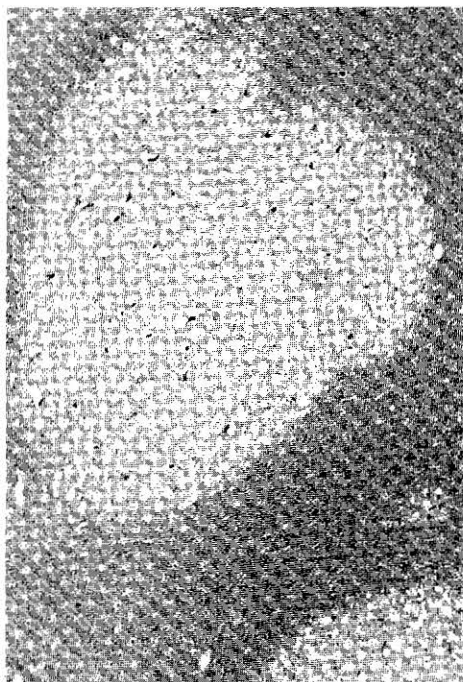


Fig. 5-63. Saluki spongiform disorder. Spongy change in the interpositus and fastigial nuclei, cerebellum. (H&E, $\times 35$.)

order of thiamine metabolism was one avenue to pursue in the Bull Mastiff syndrome. It may be relevant that similar nuclear lesions have been produced in dogs by the administration of monoamine oxidase inhibitors.¹⁶⁸

Two **Malinois shepherd-cross puppies** developed generalized tremors at 3 weeks of age.¹⁶⁹ When examined 2 weeks later, balance deficits and a stilted, hypermetric gait were also noted. Pathological studies revealed a widespread spongy change in the neuraxis that predominated in gray matter. The cerebral cortex, basal nuclei, brain stem, cerebellar nuclei, and gray matter in the cervical and lumbar enlargements were affected, with a vacuolar change in the neuropil, often adjacent to neurons and blood vessels. The spongy tissue was astroglial. White matter involvement was minimal, apart from folial cores in the cerebellum.

A progressive neurological disorder has been observed in young **Birman kittens**.¹⁷⁰ The affected kittens were related, and some were inbred. Paraparesis and ataxia were noted between 2 and 6 months of age. Four of the five affected kittens also had bilateral cataracts. Pathological studies revealed a spongiform change affecting the neuropil in the cerebral cortex, thalamus, caudal colliculus, oculomotor nucleus, and medulla. Wallerian degeneration was present in the spinal cord. Lesions were not found in the PNS.

References are on page 342.

NEURONAL ABIOTROPHY

Cerebellar cortical abiotrophy
Multisystem neuronal abiotrophy

The term **abiotrophy** (which means, literally, the lack of a life-sustaining nutritive factor) has been employed in human and more recently in veterinary neuropathology. The hallmark of the abiotrophic diseases is the premature demise of discrete and often functionally related populations of neurons. There is an important difference in the way this term has come to be used by physicians and veterinarians. In human neuropathology, several well-recognized neurodegenerative conditions are viewed by some investigators as *examples of* abiotrophic diseases; such include Parkinson's disease, Alzheimer's disease, and motor neuron diseases.¹ As the clinical disorders in these patients are seen in adulthood but before old age, they have been considered to reflect accelerated neuronal aging. These conditions have their neuropathological hallmarks, such as the neurofibrillary tangles and senile plaques of Alzheimer's disease and the Lewy bodies in Parkinson's disease, but they are not specific and can be encountered (albeit with lower frequency) in normal elderly subjects.¹

In contrast somewhat, a number of novel CNS disorders in animals, also distinguished pathologically by early neuronal degeneration and death, *have been named* abiotrophic diseases. In a few of them, diffuse populations are affected but the majority are "cerebellar cortical abiotrophies." In these abiotrophic conditions encountered in veterinary medicine, the neurological deficits usually begin in the first few weeks to months of life. Where sufficient numbers of affected animals have been studied, an inherited basis has been demonstrable.

Implicit in the use of the term abiotrophy in veterinary medicine is the presumption that the premature neuronal degeneration does not result from an acquired insult, such as an infectious agent or intoxication, but rather is the consequence of an intrinsic metabolic disorder. The term abiotrophy does not stipulate the nature of the metabolic derangement, and indeed this may vary from syndrome to syndrome. Thus this term should be viewed as a broad, generic classification of a group of clinically and pathologically similar disorders, ultimately to be replaced by a more specific designation.

Within the nervous system, an intrinsic lack of vitality and subsequent premature degeneration of any component of the tissue, such as the axons or the myelin sheaths, could be broadly viewed as an abiotrophic process.² In this discussion, the term is confined to its conventional application to neuronal, cell body disorders. Most neuronal abiotrophies in animals appear to be targeted at the cerebellar Purkinje

Table 5-2. Cerebellar cortical abiotrophies

| Breed | Comments | Reference |
|------------------------|---|---|
| Dog | | |
| Kerry Blue Terrier | Extrapyramidal involvement also | 7 |
| Gordon Setter | Delayed onset | 5, 6, 51 |
| Rough-Coated Collie | Extracerebellar involvement; Wallerian degeneration in brain stem and spinal cord | 52 |
| Australian Kelpie | | 53 |
| Airedale | | 54 |
| Bernese Mountain dog | | 55 |
| Bernese Mountain dog | | 56 |
| Finnish Harrier | | 57 |
| Brittany Spaniel | Atypical—very late onset (7-13 years) | 58 |
| Border Collie | | 59 |
| Beagle | Early onset | 60 |
| Samoyed | | 30 |
| Wire Fox Terrier | | 30 |
| Labrador Retriever | | 30, 61 |
| Golden Retriever | | 30 |
| Great Dane | | 30 |
| Schnauzer X Beagle | Delayed onset | 62 |
| Mongrel | | 63 |
| Chow | | 64 |
| Rhodesian Ridgeback | Diluted coat color | 81 |
| Cat | | |
| Domestic shorthair | | Two personal experiences, not published |
| Cattle | | |
| Angus | | 21 |
| | Seizures from birth, later cerebellar ataxia | 18, 19 |
| Charolais | | 20 |
| Holstein | | 13, 65 |
| Ayrshire | | 66 |
| Shorthorn | Affected from birth | 15 |
| Hereford | Affected from birth | 14 |
| Poll Hereford cross | Variable age of onset | 16 |
| Sheep | | |
| Merino | Late onset | 25 |
| Welsh and other breeds | | 22 |
| Corriedale | | 23 |
| Horse | | |
| Arabian | | 27 |
| Gotland pony | | 26 |
| Swine | | |
| Yorkshire | | 30 |
| Large white | | 31 |

Continued.

Table 5-2. Cerebellar cortical abiotrophies—cont'd

| Breed | Comments | Reference |
|----------------------------|---|------------|
| Primate | | |
| Baboon | Blind | 33 |
| Japanese macaque | Onset at 5 years of age | 32 |
| Rodents | | |
| Mouse | | |
| Beige | Chediak-Higashi disease | 34 |
| Staggerer | | 67, 68 |
| Lurcher | | 69, 70 |
| Purkinje cell degeneration | Loss of olfactory, thalamic, and retinal neurons also | 71, 72 |
| Nervous | | 73 |
| Weaver | Severe loss of granule cells in cerebellar vermis; brain is deficient in dopamine | 74, 75, 76 |
| Tortured | | |
| Leaner | Loss of granule cells, then Purkinje and Golgi cells; die when 3-4 weeks old | 34, 77, 78 |
| Stumbler | | 79 |
| Hyperspiny Purkinje cell | | 80 |
| Rat | | |
| Shaker | Progressive Purkinje cell loss; degeneration in inferior olivary nucleus also | 35 |

cell; diffuse neuronal abiotrophies are much less common. For a concise review of cerebellar development, structure, function, and disorder, see de Lahunta³ and Kornegay.⁴

Cerebellar cortical abiotrophy

Cerebellar cortical abiotrophies have been described in most of the domestic animal species and in a few rodents and primates (see Table 5-2). This table is intended to list the most important cerebellar cortical abiotrophies in animals. Some of these cases have not been reported as cerebellar abiotrophies. One diagnosis sometimes given is cerebellar atrophy, which is correct but lacks specificity. The other term often used is cerebellar hypoplasia, which indicates that the cerebellum has failed to develop to its full potential. We prefer to reserve this term for those diseases in which intrinsic or extrinsic factors alter the normal development of germinal populations of neuroepithelial cells. These include inherited disorders, nutritional deficiencies, and a variety of teratogens. Hypoplasia can result from such extrinsic factors as in utero viral infections (parvoviruses, bovine viral diarrhea, hog cholera) that produce degeneration and necrosis of populations of germinal cells, resulting

in failure to reach normal size. However, most of these also cause atrophy from destruction of already differentiated neuronal populations. The abiotrophic process is viewed as affecting the organ after it has developed its full cellular complement. Thus, the clinical hallmark of the cerebellar cortical abiotrophies (with few exceptions) is neurological normality at birth to be followed by the development of cerebellar deficits, which progressively worsen, in the post-natal period. In contrast, the viral agents (for example) which at a very precise stage of fetal life can damage the developing cerebellum, result in a cerebellar ataxia from the time of birth. Because the injury is not ongoing, the clinical deficiency tends to remain static or even very slowly improve as the animal compensates for its deficit.

Many reports of cerebellar cortical abiotrophic diseases describe multiple cases, including breeding studies, whereas others provide accounts of the disease in one litter or just single animals. Where a genetic basis has been established or proposed, it is an autosomal recessive pattern, affecting both sexes equally. Most cases have been reported in the **dog**, and in this species the disease has been investigated most extensively. The clinical manifestations are of cerebellar ataxia with head tremor, truncal ataxia, symmetrical hypermetria, spasticity, broad-based stance, and a loss of balance. In some syndromes, hindlimb dysmetria is more pronounced than that of the forelimbs. These deficits are usually progressive, but in some cases the condition stabilizes without further deterioration. The age of onset of these clinical signs is consistent for the disorder in each particular breed: for example, Australian Kelpie dogs (5 to 6 weeks), rough-coated Collies (4 to 8 weeks), and Kerry-Blue Terriers (12 to 16 weeks). The cerebellar cortical abiotrophy of Gordon Setter dogs is unusual in that the onset ranges from 6 to 24 months of age.^{5,6} Progressive cerebellar degeneration eventually results in inability to ambulate, and chronically recumbent dogs are usually euthanized.

At necropsy, loss of cerebellar size is recognized only later in the course of the disease. A cerebellar weight of less than 10% of the total brain weight is an indication of decreased cerebellar mass. In dogs sacrificed just at the time of clinical onset, cerebellar size usually is normal. With disease progression, cerebellar shrinkage is conspicuous with failure to fill the caudal fossa, diminution of individual cerebellar folia, and broadening of sulci (Fig. 5-64). Typically the involvement of the cerebellum is not uniform, beginning first in the vermis and paramedian lobules and spreading to the lateral lobules. In a sagittal section of the cerebellar vermis in Kerry Blue Terriers (and Arabian horses), the caudal lobules of the vermis are most spared. Unique to the Kerry Blue Terriers with their cerebellar cortical disease is a pallor, gelatinous change, and cavitation of the caudate nuclei.^{7,8} Bilateral areas of discoloration may also be seen in the olivary nuclei and substantia nigra in these dogs. These occur later in the course of the disease and follow the degenerative changes in the cerebellar cortex.

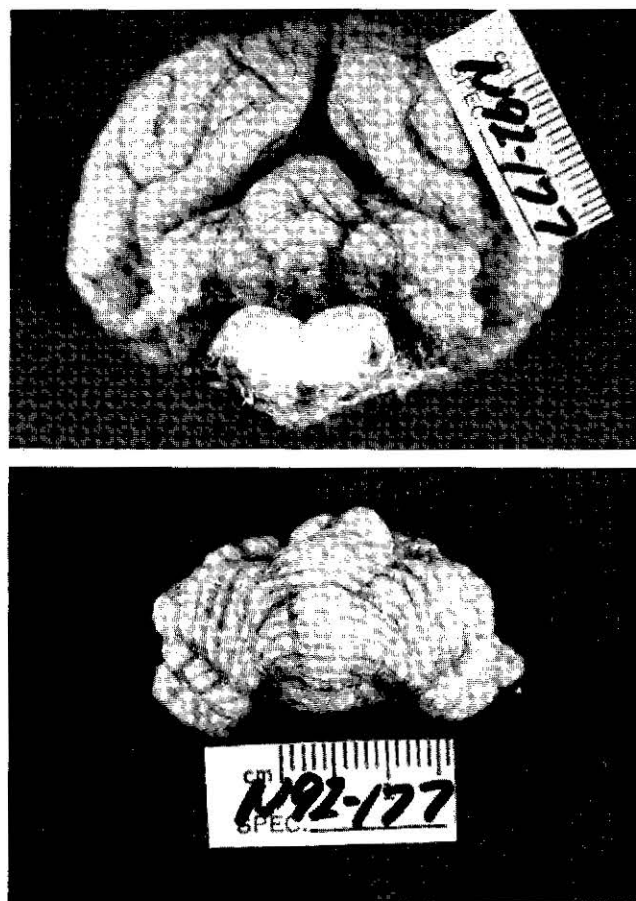


Fig. 5-64. Cerebellar cortical abiotrophy, dog. **A**, Cerebellum in situ does not fill the caudal fossa. **B**, Cerebellum separated from brain stem. Folia are sharp, especially in the hemisphere.

Microscopically, these canine (and other) cerebellar cortical abiotrophies are characterized by ongoing neuronal degeneration and loss, with reactive gliosis in a background of a normally developed cerebellum. Neither folial dysplasia nor neuronal heterotopia occurs. These are features of the in utero viral infections that can perturb normal cerebellar development in the calf, cat, piglet, and rat. Rather, one is impressed with areas of normal-appearing cerebellar cortex that merge into folia in which there is neuronal depletion. Purkinje cells are usually first affected and are reduced in number. In such folia, persisting Purkinje cells may be shrunken, dark, and eosinophilic or swollen and chromatolytic with eccentric nuclei. That they are depleted is the most obvious feature. In general, a reduction of the granule cell neurons seems to follow the Purkinje cell loss: where severe, this is striking, particularly if compared with unaffected folia (Fig. 5-65). Shrinkage of the molecular layer in severely affected areas is also found. A proliferation of astroglia (Bergmann astrocytes) is seen in folia where significant Purkinje cell loss has occurred and the molecular layer is mildly gliotic. As a consequence of Purkinje cell

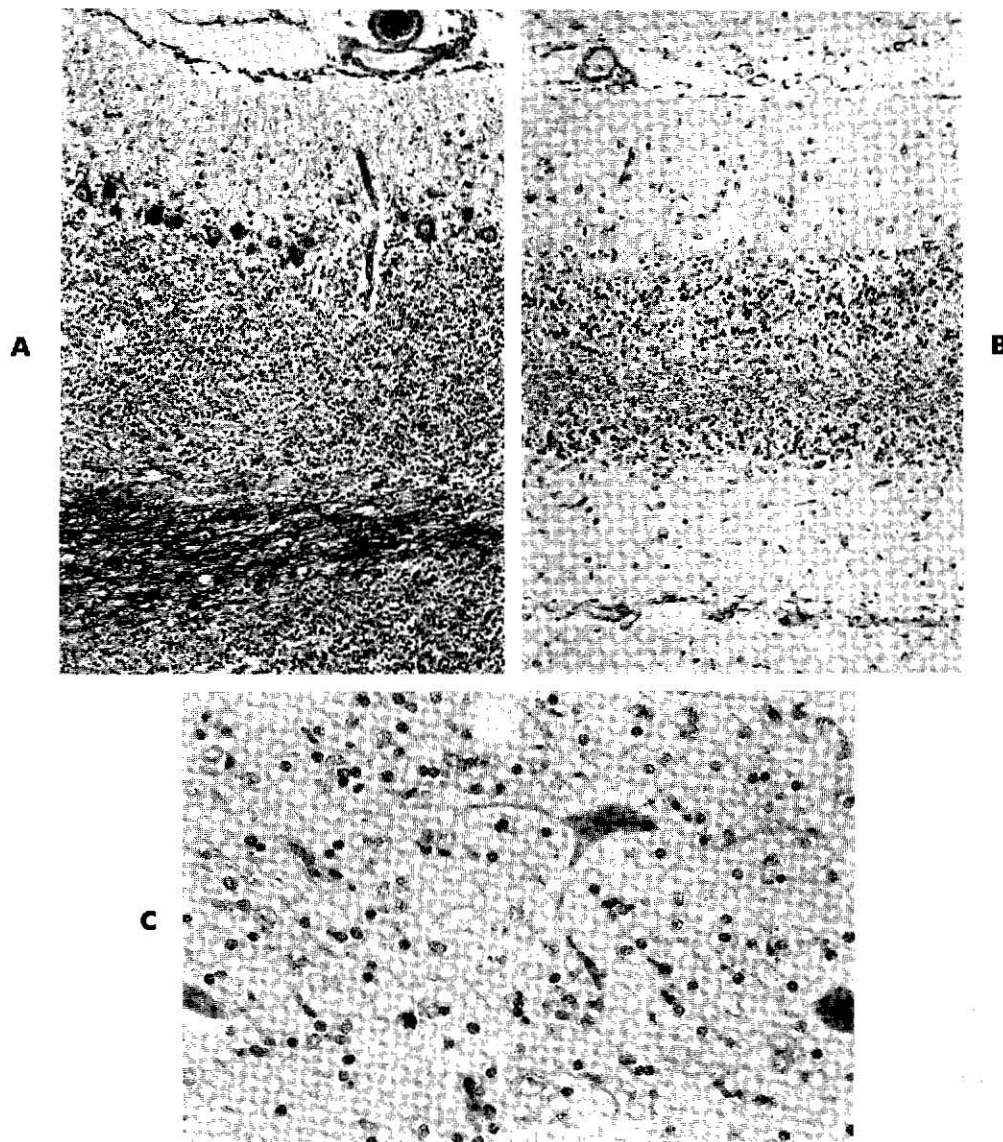


Fig. 5-65. Cerebellar cortical abiotrophy, dog. **A**, Normal cerebellum. (Luxol fast blue, cresyl echt violet, $\times 140$.) **B**, Affected cerebellum at the same magnification. Note the absence of Purkinje cells and the severely attenuated granule cell layers. (LFBCEV, $\times 140$.) **C**, Gliosis in cerebellar nucleus. (H&E, $\times 350$.)

degeneration, Wallerian degeneration may be found in the white matter of the folia. A few spheroids may also be encountered in the projection of Purkinje cell axons, namely, the granule cell layer, cerebellar white matter, or the nuclei of the cerebellar medulla. In most cases, putative retrograde (olivary) or trans-synaptic (cerebellar) nuclear degeneration is lacking, unlike comparable human disorders. The cerebellar nuclei are often gliotic, however. Following the degeneration of Purkinje cells in the Kerry Blue Terrier, neuronal chromatolysis, depletion, and pronounced vacuolation of the neuropil, which progresses to cavitation, occur in the olivary nuclei. There is also "ischemic" neuronal change and liquefaction in the caudate nucleus and vacuolar de-

generation with neuronal loss and astrogliosis in the substantia nigra. This combination of lesions is a feature of only the Kerry Blue Terrier syndrome. It has been hypothesized that a disorder of glutamate metabolism results in excitotoxic injury to Purkinje cells and neurons of the caudate nucleus, with secondary degeneration in the olives and substantia nigra, respectively.⁸ In some forms of canine cerebellar cortical abiotrophy, such as the Kerry Blue Terrier and rough-coated Collie, Wallerian degeneration is found in the lateral and ventral funiculi of the spinal cord.

Few ultrastructural studies of this group of diseases have been reported. Montgomery and Storts⁹ examined the Kerry Blue Terrier and found early lesions in Purkinje cell den-

drites. Dendritic stems contained cytoplasmic lamellar bodies and abundant enlarged mitochondria with electron-dense matrices. That the dendritic segment is first affected is of considerable interest as the excitotoxins are known to first affect neuronal dendrites,¹⁰ although classically they produce watery changes. These Purkinje cell dendrites degenerated and disappeared, but stages of degeneration in the soma were much more difficult to document. Neurons of the caudate nucleus acquired lipid droplets and developed degenerative changes in their dendritic zones similar to those of Purkinje cells. Terminal necrosis of caudate neurons was marked by contracted pyknotic nuclei and granular, structureless cytoplasm. Processes of astrocytes were swollen. In the Gordon Setter disease,¹¹ Purkinje cells and granule cell neurons undergo a progressive loss of nuclear and cytoplasmic volume, degenerate, and disappear. Cerebellar glomeruli are depleted of granule cell dendrites, and, in their stead, filament-laden astroglial processes are found in association with mossy fiber axon terminals. Large multipolar neurons in the cerebellar nuclei contain fewer surface synapses than those in control animals, as well as degenerating axons and astrogliosis. Whether granule cell loss occurs secondary to a primary effect on Purkinje cells or both populations are primary targets awaits clarification. Synaptic neurochemical changes, observed in Gordon Setter dogs between 6 months and 5 years of age, have been recorded.¹²

In comparison to the dog, cerebellar cortical abiotrophies are exceptionally uncommon in the **cat**; we have observed a single case. In contrast, several examples are recognized in **cattle** (see Table 5-2). Differentiation from the effects of in utero infection with bovine virus diarrhea is important. This is not difficult in those abiotrophic disorders in which calves are not affected until several months of age (e.g., in Holsteins¹³). However, in some cases, calves are affected at or within a week of birth.¹⁴⁻¹⁶ We still view these latter examples as abiotrophic diseases, but with unusually early onset. The pattern of neuropathological changes is characteristic of this group of diseases and quite different from the destructive effects of BVD virus.

Clinically, calves with cerebellar cortical abiotrophy develop head tremors, a basewide stance, and a hypermetric, spastic gait. Frequently, they suffer from a severe lack of coordination and balance, resulting in repeated falling and prolonged periods of recumbency. Grossly, the cerebellum from affected calves may appear normal or wasted. Microscopic cerebellar cortical changes are as for the dog. In some syndromes (Holstein) there are vacuolar changes in the neuropil and neuronal chromatolysis in the cerebellar nuclei. A unique finding in the Hereford calves described by Innes and associates¹⁴ was a population of neuroblasts within the molecular layer. These presumably are a population of neuronal progenitors, arrested in the course of their normal migration.

A neurological syndrome, perhaps now primarily of his-

torical importance, has been described affecting **Aberdeen Angus cattle** in Scotland. The disease has been controlled by elimination of cattle that transmit the disorder;¹⁷ it may, however, appear elsewhere in the world in Angus cattle.

The clinical signs are unusual in several respects. Affected calves, some within a few hours of birth,¹⁸ have repetitive episodes of seizure activity. Seizures vary from stiffness of the limbs, neck, and tail, to collapse, opisthotonic posture, and rigid spasm. In calves 2 or 3 months of age surviving episodes of seizures, the gradual development of a cerebellar ataxia ensues with a stiff, spastic gait and basewide stance. By 15 months, seizures have declined, leaving the residual ataxia, which may also resolve in cattle older than 2 years of age.¹⁹

Pathological changes are confined to the cerebellum, both in the early¹⁸ and later¹⁷ phases, and are microscopic. The youngest affected convulsing calves lack morphological changes. In older animals, changes in the soma and axons of Purkinje cells are progressive with the clinical course. Purkinje cells are vacuolated, swollen, and chromatolytic, either individually or in groups; others are shrunken and densely stained with a swollen, eccentrically located nucleus. Axonal swellings (torpedoes) involve the Purkinje cell axons, particularly the proximal segments. There is mild Wallerian degeneration in cerebellar folial white matter. Lysis of Purkinje cells leaves empty baskets with a modest reactive astrocytosis; surprisingly, changes in the relay nuclei are minimal.

Electron microscopic studies have revealed an early proliferation of tubulovesicular elements and progressive accumulation of mitochondria and neurofilaments within swollen axons. Myelin sheaths are attenuated over swollen axons, some of which progress to collapse and necrosis.

Although breeding studies are somewhat inconclusive, this is thought to be inherited as an autosomal dominant disorder with incomplete penetrance.¹⁹ The pathogenesis is entirely obscure. Biochemical studies of plasma, urine, and CSF from affected calves have been unrewarding.

This condition is perhaps unique in its clinical metamorphosis from seizures to residual ataxia to apparent recovery. Furthermore, it seems unlikely that the initial expression can be ascribed to a cerebellar disorder, as seizures usually reflect prosencephalic disorders. A single case of a somewhat similar disorder was encountered in a Charolais calf.²⁰ The animal had episodes of seizures from about 6 months of age and subsequently developed a spastic cerebellar ataxia.

In Angus calves in the United States, a cerebellar abiotrophy with clinical onset at approximately 7 months of age has been observed.²¹ Signs were referable to cerebellar disorder, and seizures were not observed. Purkinje cell degeneration and loss were the major pathological findings in these three calves.

What were probably examples of cerebellar cortical abiotrophy in **sheep** were described in various breeds in Britain,

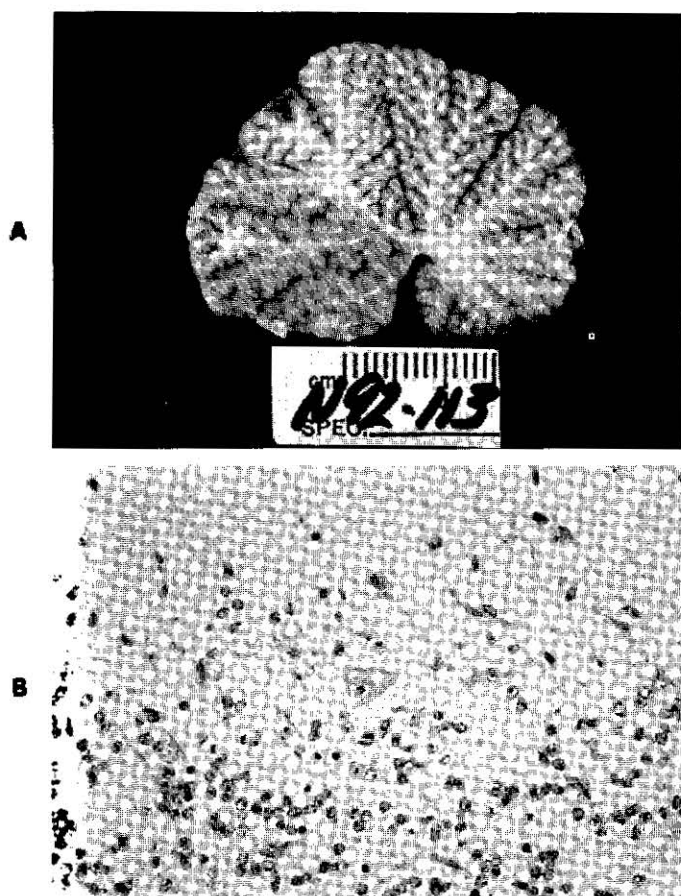


Fig. 5-66. Cerebellar cortical abiotrophy, horse. A, Median section of cerebellum. Caudal lobules (to left) are best preserved. B, A single Purkinje cell and depleted granule cell layer. (H&E, ×350.)

including Welsh and Welsh mountain sheep, and in Canadian Corriedale lambs.^{22,23} The disease in England has become known colloquially as daft lamb disease. A clinically similar syndrome has been described in Border Leicester lambs that have skeletal fragility and a myopathy but no cerebellar or other CNS abnormalities.²⁴ Cerebellar cortical abiotrophy in Australian Merino sheep affected animals 3.5 years of age or older.²⁵ Clinical and neuropathological features were as previously described. There was also depletion of neurons and gliosis of the nuclei of the cerebellar medulla and the vestibular nuclei, as well as mild to moderate Wallerian degeneration of brain stem and spinal cord white matter.

In horses, cerebellar cortical abiotrophy (Fig. 5-66) has been described in the Swedish Gotland pony²⁶ and in Arabian and part-Arabian foals.²⁷⁻²⁹ Clinical signs may be present from birth or may not develop until 9 months of age. The degree of ataxia is variable, with the worst affected foals unable to stand. The dysmetria is accompanied by a remarkable degree of spasticity. There is fine head tremor and lack of menace response. An autosomal recessive in-

heritance has been proposed for the Gotland pony and presumed for the Arabian foals. In Yorkshire pigs progressive cerebellar disease has been observed, appearing between the fourth and fifth weeks of life.³⁰ Commonly within a week of onset, coordination of movement has so deteriorated that affected piglets cannot stand normally. The neuropathological findings are unusual; many Purkinje cells have swellings of their proximal axonal segments (torpedoes) within the granule cell layer while the perikaryon appears unremarkable. In England, a congenital neurological disorder was seen in the progeny of a large white boar.³¹ In affected litters, 25% of the piglets from birth had difficulty in standing, made ataxic and dysmetric movements, trembled, and frequently fell. Microscopic findings were classical with a reduction of Purkinje and granule cell neurons. There were also Purkinje neuron axonal swellings. These changes progressed with increasing age.

Few comparable cerebellar diseases have been described in nonhuman primates. In an approximately 5-year-old Japanese macaque with an intentional head tremor, cerebellar Purkinje cell and granule cell degeneration and depletion were found.³² Similar changes were observed in a juvenile baboon that was apparently blind and had progressive ataxia and seizures.³³

An impressive number of inherited cerebellar disorders have been recognized in mice. Typically, degenerative changes begin very early in life, but they conform more or less to our concept of abiotrophic disease. In the review by Sidman³⁴ are listed the genetic background of these mutants and the affected chromosome, if known. They are often named to describe the gait and so include **staggerer**, **lurcher**, **nervous**, **weaver**, **tortured**, **leaner**, and **stumbler**. Many have been extensively studied by Golgi techniques and electron microscopy. Progressive Purkinje cell degeneration has been described in the shaker rat.³⁵

Multisystem neuronal abiotrophy

The progressive degeneration and loss of cerebellar cortical neurons, usually resulting in clinical presentation of the patient in early life, is the hallmark of the neuronal abiotrophies in animals. In humans, a similar pattern of neuropathological changes is seen in a number of conditions that, in contrast, present in early to middle adulthood. In these diseases, there is usually a concurrent degeneration of other neuronal populations. For this reason, these human disorders are classified within a broad group of neurodegenerative diseases referred to as the **systems degenerations**. Human systems degenerations include both familial and acquired conditions and may affect single or multiple neuronal systems, including motor, sensory, and autonomic neurons and populations located in the basal nuclei. A few conditions are predominantly cerebellar, such as **Holmes cerebello-olivary degeneration**, which affects Purkinje cells, granule cells, and neurons in the olivary nuclei. There are mixed cerebellar, brain stem, and spinal forms, such as

olivopontocerebellar atrophy, in which Purkinje and granule cells, neurons in the olivary and pontine nuclei, substantia nigra and putamen, and tracts in the dorsal columns of spinal cord all degenerate. Some human cerebellar ataxias are associated with metabolic disorders, including ataxia-telangiectasia, Refsum's disease, and abetalipoproteinemia.

A few neuronal abiotrophies of animals affect diffuse populations and can be viewed as systems degenerations. **Hereditary porcine neuronal system degeneration (HPNSD)** was originally encountered in the litter of a cross-bred sow in 1983. Subsequent breeding studies established that the disorder has an autosomal dominant pattern of inheritance.³⁶ Usually beginning by 20 weeks of age with pelvic limb tremor and truncal ataxia, the severity and extent of progression of neurological deficit vary from case to case. Some pigs deteriorate to a state of tetraplegia, but mildly affected animals can be reared to breed. Neuropathological findings are of bland dissolution and fading away of the neuronal perikaryon of spinal cord motor neurons. The affected perikarya, which may be difficult to identify, are highlighted by a satellitosis of astrocytes and their processes. Lower motor neuron loss results in Wallerian degeneration in the ventral nerve roots and peripheral nerves. Degeneration is also found in the dorsal spinocerebellar and ventral sulcomarginal tracts of the spinal cord. Ultrastructural examination of ventral gray column neurons in HPNSD reveals vesicular mitochondria with abnormal cristae and electron-dense inclusions. Although designated a neuronal system degeneration, it may be more appropriate at this stage to view the disorder as a lower motor neuron disease.

In the neuronal abiotrophy of the **Swedish Lapland reindeer-herd dogs**, there is degeneration of dispersed motor and sensory neurons. The clinical signs in this recessively inherited disease are referable to involvement of the somatic motor neurons. Signs first appear at 5 to 7 weeks as weakness in the forelimbs or hindlimbs. Progression is rapid, and within 2 weeks the pups are in sternal recumbency and unable to rise. Muscle wasting is pronounced in the distal muscles of limbs, resulting in fixation of joints and limb deformities from the shortening of denervated muscles. Electromyography reveals denervation potentials. Tetraparetic dogs may survive to adulthood, but some have died with bronchopneumonia and others have been euthanized.

Although the clinical picture is that of a lower motor neuron disease, pathology studies reveal a neurodegenerative process that extends beyond the motor neurons. In keeping with the distribution of muscle weakness and wasting, spinal neurons in the lateral portion of the ventral horns of the cervical and lumbosacral spinal cord intumescences were affected severely. Many neurons appeared to have undergone central chromatolysis. In some perikarya the loss of Nissl substance was peripheral, and others appeared to be undergoing neuronophagia. Degeneration of motor axons was observed in the ventral roots. Chromatolytic neurons were also frequent in the spinal ganglia, and degeneration appeared along the central projections of these sensory neu-

rons in the dorsal horns and dorsal funiculi of the spinal cord. Axon degeneration was also encountered in the ventral and lateral spinal funiculi. It was intense in the regions of the dorsal and ventral spinocerebellar tracts. Degenerative changes in the brain were most striking in the cerebellum, where chromatolytic and atrophic Purkinje perikarya were associated with dense axonal degeneration in the medullary rays of the folia and in the cerebellar nuclei.

Studies to date^{37,38} have not included ultrastructural evaluation. The site of the initial defect and the sequence of the cytological changes in this neurodegeneration remain to be defined. Although this canine disease presents clinically as a spinal muscular atrophy, a comparison with Werdnig-Hoffmann disease in infants seems tenuous, especially in view of the involvement of more diverse neuron populations.³⁹ Comparatively, this canine abiotrophy would seem to have more in common with the cases of infantile neuronal degeneration that masquerade as Werdnig-Hoffmann disease.⁴⁰

A neurodegenerative disorder has been observed in **Cairn Terriers** in the United Kingdom,⁴¹ Australia,⁴² and North America.⁴³ As in Lapland dogs, this degeneration affects diverse neuronal populations. The clinical signs, which appear at 5 months of age or earlier, progress from episodic pelvic limb collapse at the onset to persistent paraparesis with patellar areflexia, tetraparesis, hypermetria, and head tremor. In the two Cairns that we have examined, bouts of hypotonic collapse resembled cataplexy. The initial signs of hind limb weakness in this breed have led to confusion with globoid cell leukodystrophy (Krabbe's disease).

As in the aforementioned degenerations, there were chromatolytic perikaryal changes. Although the Nissl loss was most striking in large cell bodies, like the somatic motor neurons (Fig. 5-67), this change was widespread. Chromatolytic perikarya occurred in the cerebral cortex, the red nucleus, some thalamic nuclei, the cerebellar nuclei, brain stem reticular nuclei, and the nucleus thoracicus and proprius of the spinal cord, as well as in spinal autonomic neurons. Affected cell bodies were swollen and variably chromatolytic. In many spinal motor neurons, the Nissl loss was peripheral; in the red nucleus, central chromatolysis was usual. In some cell bodies, the chromatolysis was complete; in others, it was patchy or irregular. At the ultrastructural level, the Nissl-depleted neurons were characterized by dispersion and loss of ribosomes. Although some neurons contained aggregated neurofilaments in the areas of Nissl loss, others were marked by watery cytoplasm with widely scattered filaments. Some of the latter neurons contained swollen vesicular profiles of ribosome-depleted endoplasmic reticulum. These vesicles resembled the degenerative dilations of the endoplasmic reticulum and Golgi complex that characterize the chromatolytic neurons in the wobbler mouse, a murine model of lower motor neuron disease.^{44,45} In the early stages of this disease, changes were encountered at far greater frequency in cell bodies than in axons. Unlike the axon reaction, there were no indications of a regenerative

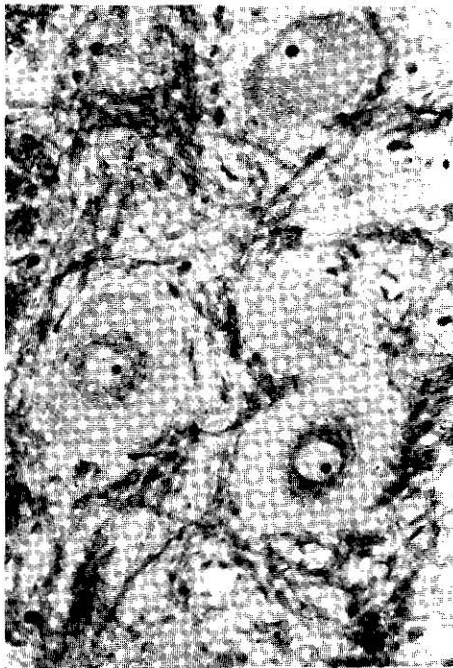


Fig. 5-67. Cairn neuronopathy. Central and peripheral chromatolysis, spinal cord. (Luxol fast blue, cresyl echt violet, $\times 350$.)

capacity in the chromatolyzed neurons; that is, there was no diffuse cytoplasmic basophilia, no nucleolar hypertrophy, and little or no nuclear cap formation.⁴⁶ Instead, the affected cell bodies more closely resembled the degenerating chromatolytic neurons of Werdnig-Hoffmann disease.⁴⁷ In one pup with very early and severe signs, the chromatolytic changes were accompanied by poliomalacia and leukomalacia that appeared symmetrically in the dorsal horns and adjoining funicular white matter of thoracolumbar spinal segments.⁴⁸ The metabolic derangement that resulted in widespread chromatolytic degeneration and focal myelomalacia has not been identified.

A slowly progressive diffuse neurodegenerative disorder of young adult red-haired **Cocker Spaniel dogs** has been described by Jaggy and Vandeveldt.⁴⁹ The four affected dogs, presenting between 10 and 14 months of age, shared a common male ancestor. Some months prior to their clinical examination, these dogs began a course of gait abnormalities, balance loss, and abnormal behavior. Their nature varied from apathetic to aggressive, and normal learned conduct, such as house training, was lost. Neurological examination conveyed the impression of anxious animals that were easily startled by visual or auditory stimuli. The gait was hypermetric and ataxic, and there was intention tremor.

As anticipated, neuropathological changes were widespread in the brain. Primary changes were considered to be nerve cell degeneration and loss, with an accompanying gliosis; such changes affected the septal area, the basal nuclei (globus pallidus), diencephalon (medial geniculate bodies, subthalamic nuclei), midbrain (tectum, substantia

nigra), and nuclei of the cerebellum. A few axonal spheroids were also found in these neuronal centers. White matter pallor, severe gliosis, and axonal dystrophy particularly affected white matter of the cerebellar medulla, corpus callosum, and thalamus.

This familial, multisystemic neuronal degeneration in Cocker Spaniel dogs is manifest clinically as cerebral and cerebellar deficits. An intrinsic disorder of neuronal metabolism is suspected.

Two male pups from a litter of three **Miniature Poodle dogs** were unable to attain normal posture from recumbency. This condition worsened such that by 7.5 weeks of age they rolled, thrashed their limbs vigorously, and had head tremors. Examination of each brain, following euthanasia, revealed a slightly small cerebellum. Microscopically, degeneration in the cerebellum and the cerebral cortex was found, most severely affecting cerebellar Purkinje neurons, particularly in the dorsal vermis. Neuronal changes were either of cytoplasmic pallor and vacuolation or of shrinkage accompanied by marked cytoplasmic eosinophilia and nuclear pyknosis. Sometimes swollen Purkinje cell dendrites were conspicuous within the molecular layer. Where Purkinje cell numbers were depleted, astroglia were more numerous, and granule cell neurons were thinned. Cell loss also depleted the lateral nucleus in the cerebellar medulla. Similar vacuolar and hyperchromatic changes affected cerebrocortical neurons, although less severely. Ultrastructural studies revealed the basis for this dual pattern of neuronal alteration: Vacuolar Purkinje cells resulted from distended cisternae of endoplasmic reticulum, whereas hypereosinophilic cells bore abundant swollen mitochondria and many condensed stacks of granular endoplasmic reticulum that had been transformed into lamellar bodies. These lamellar bodies, or tubular variants, were also found within Purkinje dendrites and axons. Whether this neurodegenerative disorder of these two neonatal Miniature Poodle pups is inherited or acquired is yet to be established.⁵⁰

Progressive degeneration of cerebellar and brain stem nuclei and spinal cord degeneration are described in the **vibrator** and **cerebellar outflow degeneration** mutations in mice.³⁴

References are on page 346.

MOTOR NEURON DISEASES

Introduction—man

Motor neuron diseases

dog—Stockard's paralysis, New Zealand dogs, Swedish Lapland, Pointers, German Shepherds, Doberman horse, cat, goat, mice

Motor neuron diseases with neurofilamentous accumulation—introduction

rabbit

dog—Brittany Spaniel, Rottweiler

pigs, cattle—Hereford, Brown Swiss, Red Danish

The **motor neuron diseases of humans** cover a spectrum of degenerative disorders with onset varying from the neonatal period to late adulthood. Their classification varies somewhat from one side of the Atlantic to the other. Suffice it to say that **amyotrophic lateral sclerosis (ALS)** is the most important and that progressive muscular atrophy and progressive bulbar paralysis are viewed either as variants of ALS or all three diseases are perceived as a continuum. In ALS, degeneration leading to loss of the neuronal perikaryon and its processes involves both upper and lower motor neurons. Patients present, usually in middle age, with progressive, ascending (distal to proximal) weakness and muscle wasting. Most cases are sporadic. In contrast, the **infantile spinal muscular atrophies (ISMA)** involve only the lower motor neuron (anterior horn of the spinal cord and certain brain stem nuclei), are manifest early in life, and are inherited. **Werdnig-Hoffmann disease** and the milder **Kugelberg-Welander syndrome** are examples of the spinal muscular atrophies. The spectrum of spontaneous or contrived motor neuron diseases of animals, which may be of value as models of ALS and ISMA in humans, have been reviewed.¹

In this section, we are concerned with motor neuron diseases of animals, which are largely of lower motor neuron (LMN) type, and particularly those with a familial basis. Hallmarks of several of these disorders are abnormal neurofilament accumulation in the neuronal perikaryon, in the proximal axonal segment, or in both sites, and their inappropriate phosphorylation.² In other conditions to be discussed first, neurofibrillary accumulation is not the predominant feature. Perhaps the first motor neuron disease described in animals was **Stockard's paralysis of dogs**.³ This disorder occurred in the course of endocrine studies of Great Dane and St. Bernard dogs when hybrids of these two breeds, and of Great Dane-Bloodhound crosses, were produced; the disease is largely of historical interest. At 11 to 14 weeks of age, affected progeny developed variably severe pelvic limb paresis or paralysis. The deficit developed over a few days and then remained static. Distal limb muscles were particularly affected, while the head, neck, and trunk were spared. Pronounced degenerative and gliotic changes were found in lumbar segments of the spinal cord with depletion of somatic motor and preganglionic sympathetic neurons.

In 1963, Hartley⁴ described **9 dogs with LMN disease** in New Zealand, seven of which were only 3 to 9 months of age. These animals presented with pelvic limb paresis of abrupt onset, which in most cases progressed within a few weeks to flaccid paraplegia or tetraplegia. Atrophy of musculature was marked, either diffusely in the dogs that developed tetraplegia or was more localized. Postmortem findings were loss of motor neurons from the ventral gray column of the spinal cord but sparing the brain. Empty spaces were the landmarks to cell bodies that had degenerated while the prior site of others was marked by glial stars. In tetraplegic dogs, motor neurons were depleted in cervical, thoracic,

and lumbar segments. Accompanying this loss of cell bodies was a Wallerian degeneration in the ventral spinal roots and spinal nerves, which appeared to be more severe distally. The cause of this LMN disease was not established, but a nutritional deficiency or an intoxication was suggested.

An hereditary neuronal abiotrophy has been described in the **Swedish Lapland reindeer-herd dog**⁵ and has been compared to infantile spinal muscular atrophy.⁶ The clinical presentation is that of LMN disease, but studies have revealed a neurodegenerative disorder involving dispersed neuronal populations. When first reported, the disorder was designated a neuronal abiotrophy, and it is discussed with those diseases.

Progressive neurogenic muscular atrophy in Pointer dogs, which has an autosomal recessive mode of inheritance, appears clinically as pelvic limb weakness at 18 to 23 weeks of age.^{7,8} In affected English Pointer pups, the onset is signaled by trembling in the hindlimbs. This mild weakness progresses quickly to stumbling, falling, and then recumbency. Recumbent animals initially rest on their sternums and are unable to rise. Later, fasciculations appear, and the dogs lapse into lateral recumbency with little voluntary movement, as muscle wasting and contractures develop in the limbs. Spinal reflexes are diminished, and dysphonia is also detected. Electromyographic evidence of denervation is first recorded at 5 months in the distal muscles of the forelimb and then progresses to the hindlimbs and proximally. Many pups die or are euthanized before 1 year of age.

Pathology studies have provided ample evidence of neurogenic atrophy, especially in the distal muscles of the limbs. Correspondingly, evidence of axonal degeneration was most prevalent in the distal course of the peripheral motor nerves. At this level, the presence of Büngner's bands suggested that the loss of axons existed for some time. In the ventral spinal roots, there was less evidence of axon degeneration, and the presence of fragmented axons with myelin debris and macrophages indicated more recent or ongoing degeneration. On microscopic examination of the spinal cord, the ventral horn cells seemed to be present in normal numbers. These perikarya, however, as well as those of the hypoglossal and spinal accessory nuclei in the brain stem, contained large accumulations of 1 μ m to 3 μ m, alcohol-insoluble granules that stained with Sudan black B, Luxol fast blue, and Alcian blue. At the ultrastructural level, these granules consisted of multilamellar membranous arrays.⁹ In some, the lamellae were concentrically arranged and resembled closely the membranous cytoplasmic bodies that are typically found in the ganglioside storage diseases. In other inclusions, the lamellae were arranged in parallel and were identical to the zebra bodies that are found usually in the mucopolysaccharidoses. These inclusions, which also occurred in the dendrites and axons, were thought to reflect a primary abnormality in the lipid metabolism of lower motor neurons that leads to axon degeneration. It remains to be determined whether this is a variant of a known storage

disease. This possibility has been suggested by reports in humans of a variant form of hexosaminidase A deficiency in which signs of spinal muscular atrophy predominate.^{10,11}

Spinal muscular atrophy in German Shepherd dogs is an LMN disease that differs from those recorded previously in domestic animals in that the ventral horn cell degeneration is asymmetric and confined to segments of the cervical intumescence.¹² This disorder, which was identified in a kennel that practiced line breeding, may have an hereditary basis.

Affected pups have been of both sexes. They develop normally up to the age of 12 to 14 days, when forelimb weakness becomes evident. This weakness is bilateral but asymmetric, or unilateral. Weakness is followed quickly by wasting of the antebrachial and/or brachial muscles. Contractures also develop, resulting in valgus and flexion deformities of the carpus. When forelimb paresis is bilateral, it results in an inability to rise from sternal recumbency, nursing difficulties, and flattening of the thorax. Contractures and carpal deformity have been treated by tenotomy and splinting in one pup in which the paresis was unilateral and limited to the forearm muscles.

On gross inspection at necropsy, the denervated forelimb muscles were atrophied and discolored. The neural lesions responsible for the muscle changes resided within the cervical intumescence and consisted of asymmetric but marked loss and degeneration of the somatic motor neurons. The loss of neurons was often striking in the lateral portion of the ventral horn, that is, lamina IX of Rexed. In the most severely affected segments, few motor neurons survived, and the ventral horn was scarred by proliferated astrocytes. Of the surviving neurons, most appeared to be undergoing peripheral chromatolysis without obvious enlargement. Other affected cell bodies contained vacuoles, and shrunken perikarya occasionally underwent neuronophagia. The regression of motor perikarya was associated with degeneration and loss of motor axons in the small, intraspinal fascicles that vertically traverse the ventral funiculus enroute to form the ventral rootlets. With myelin stains, the ventral rootlets of the affected segments were much paler than the dorsal rootlets. The ventral rootlets contained many cords of proliferated Schwann cells—that is, Büngner's bands—that formed in the wake of axon degeneration. These bands en masse gave the motor rootlets and roots a highly cellular appearance. Because the primary sensory neurons were not affected, the proportion of degenerated axons decreased distal to the point where the dorsal roots converged with ventral roots to form the spinal nerves. Nevertheless, the branches of the brachial plexus and the forelimb peripheral nerves contained clusters of Büngner's bands, associated macrophages, and increased amounts of endoneurial collagen. Electron microscopic study of limited numbers of degenerating ventral horn neurons revealed a dispersion and loss of free and attached ribosomes in the peripheral cytoplasm. Some of the chromatolytic cell bodies contained seemingly few mitochondria and multilocular membranous vacuoles

of unknown origin. Increases in perikaryal or axonal neurofilaments were not seen. The observed reduction in ribosomes betokens an impaired capacity to synthesize protein, but this impairment may not be of primary significance in the pathogenesis of this neuronopathy.

We have observed a motor neuron degeneration affecting two male **Doberman pups** from a litter of eight. Signs that appeared at 4 weeks as pelvic limb weakness eventuated in more severe paresis and wasting in the forelimbs. Pathological studies revealed degeneration in bulbar and spinal motor neurons as well as other brain stem nuclei, such as vestibular and reticular nuclei. Affected cell bodies were chromatolyzed or vacuolated in paraffin sections. Ultrastructural studies showed profound vacuolar change in the perikaryon, apparently derived from the rER.

In contrast to the preceding diseases, which have an established or suspected hereditary basis, an **equine motor neuron disease** identified in the United States¹³ appears to be an acquired disease. Both sexes have been affected, and animals have ranged in age from 15 months to 25 years. Thoroughbreds, Standardbreds, Quarter horses, Appaloosas, Walking horses, Arabians, a Morgan, a pony, and various mixed breeds have developed this disorder, which is characterized by weakness, muscle fasciculations, muscle atrophy, and weight loss.^{14,15} Signs usually progressed over several months. The first animals studied were from farms in the northeastern states (New York, Pennsylvania, Connecticut, and Vermont), but the disease is widely distributed in North America. Cases have recently been recorded in Europe.^{16,17} Usually only one horse is affected at a stable. The signs of this illness, many of which reflect weakness, were expressed in a cautious, short-strided gait. Trembling and spending large amounts of time in recumbency were also common manifestations of weakness. Many affected horses stood with their feet camped under the body and their heads hung because of cervical weakness. Muscle fasciculations were often visible. Mild exercise seemed to accentuate trembling and sweating. Signs of hyperesthesia or pain were evinced in some animals by light touch or palpation. In the majority of the cases, the horses were unable to stand without frequently shifting their weight from one limb to the other, probably reflecting weakness and perhaps discomfort. Although many owners have requested that animals be euthanized as the weakness grew progressively worse, a few horses reached the point where they were permanently recumbent and these died spontaneously. In a growing number of animals, however, the progression of clinical signs has arrested or abated, leaving these animals disabled to varying degrees. Despite severe motor neuron disease, all animals maintained very good or even excessive appetites. Serum creatine kinase levels were often mildly elevated during the progressive phase of the illness. Lumbosacral CSF sometimes contained mildly elevated protein levels. Typically, EMG has revealed diffuse denervation potentials.

Aside from marked muscle wasting with prominent dis-

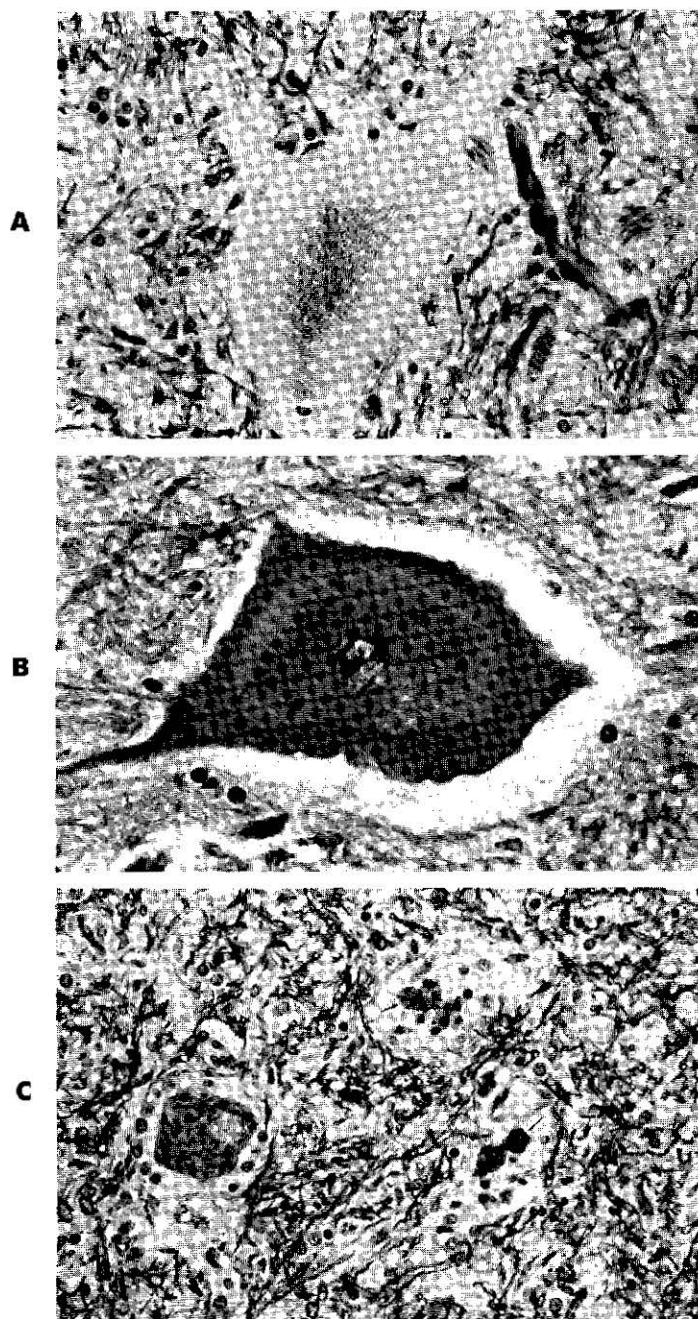


Fig. 5-68. Equine motor neuron disease. **A**, Chromatolytic neuron, spinal cord. (Luxol fast blue, cresyl echt violet, $\times 350$.) **B**, Degenerate, shrunken neuron with fragmenting nucleus and cytoplasmic inclusions. (H&E, $\times 560$.) **C**, Macrophages laden with lipofuscin (arrows) are found in the wake of motor neuron loss. (LFBCEV, $\times 350$.)

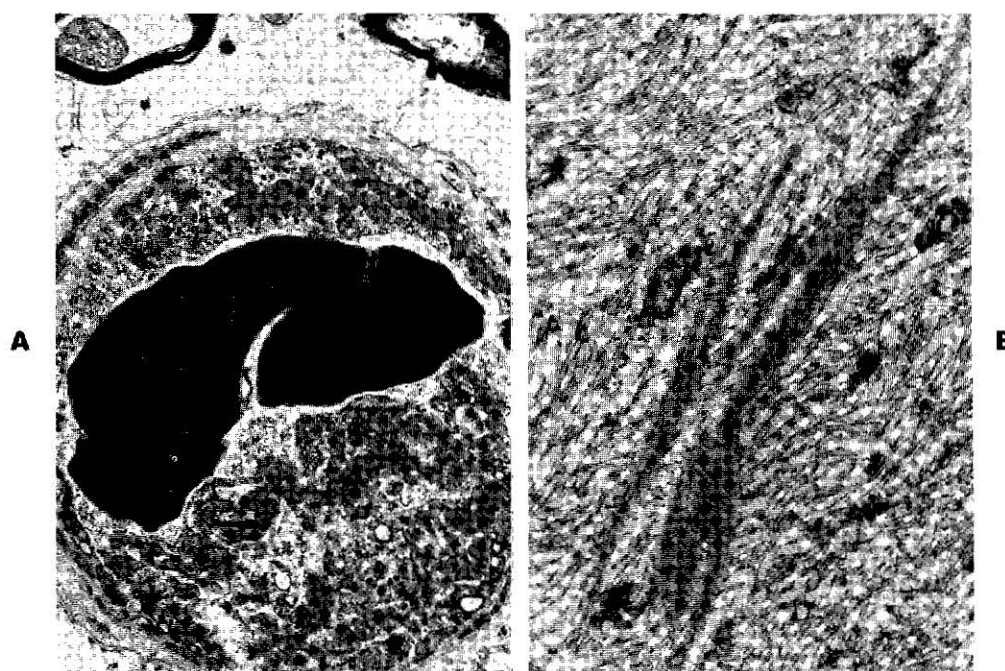


Fig. 5-69. Equine motor neuron disease: electron microscopy. **A**, Lipopigment in endothelial cells, spinal cord. ($\times 12,500$.) **B**, Hirano body, consisting of arrays of fine filaments, within an axon. ($\times 37,500$.)

coloration, most evident in the medial head of the triceps brachii and vastus intermedius, there were no consistent gross findings at necropsy. In all affected animals, microscopic study has revealed degeneration and/or loss of somatic motor neurons in the spinal ventral horns (Fig. 5-68) and angular atrophied skeletal muscle fibers. During the progressive phase of the disorder, many motor neurons were swollen and chromatolytic. Pale, swollen neurons without visible nuclei appeared as ghost cells. When present, nuclei in the swollen chromatolytic neurons were usually central or mildly eccentric. Nuclei of affected cell bodies were often irregular in outline and contained unusual, large clumps of heterochromatin. In some motor neurons, the nuclei were undergoing karyorrhexis. The cytoplasm of many chromatolytic neurons was lightly eosinophilic and sometimes contained single or multiple inclusions, which were more distinctly stained by eosin. Such enlarged chromatolytic neurons were clearly more argyrophilic than unaffected motor neurons with preserved Nissl substance. Immunocytochemical preparations revealed strong reactivity for prematurely phosphorylated neurofilaments in the swollen, Nissl-depleted ventral horn cells. Some degenerating motor neurons were shrunken and contained condensed deposits of lipofuscin. Similar lipopigment deposits have been prominent (at the ultrastructural level) in the endothelial cells of spinal cord capillaries and venules (Fig. 5-69, A). The severely shrunken irregular outlines of necrotic neurons were surrounded by microglia and were undergoing neuronophagia. Focal aggregates of pigmented microglial cells and

astrocytes formed scars at the sites of earlier neuron loss. In a few horses, some sections of the ventral horn contained thin perivenular cuffs of mononuclear cells.

Similar degenerative changes occurred in motor neurons in the brain stem. Chromatolytic swollen neurons were found in limited numbers in the hypoglossal, facial, and trigeminal motor nuclei as well as in the nucleus ambiguus. Ghost cells were also scattered within the spinal ganglia. Sensory neurons were less frequently affected than motor neurons. This was evident in the lower incidence of axon degeneration in dorsal as opposed to the ventral rootlets. Fragmented axons and spheroids were commonly found in the multiple small fascicles that convey the motor fibers through the ventral funiculus to the ventral rootlets. Microscopic examination of most spinal nerves and some cranial nerves (V, VII, XI, XII) disclosed evidence of degeneration of myelinated axons in the form of multiple digestion chambers with macrophages, broadened endoneurial expanses, and Schwann cell proliferation. In cases with arrested clinical progression, the ventral rootlets contain persisting Büngner's bands. The marked and consistent involvement of XI has provided the basis for the antemortem diagnosis of this disease by biopsy of the branch of XI that innervates the sternocephalicus muscle.

Other CNS changes were observed less frequently and inconsistently. Axon degeneration occurred to varying degrees in one or more of the spinal funiculi in all horses.

Ultrastructural studies of degenerating motor neurons revealed extensive to complete depletion of free and attached

ribosomes and moderate to marked accumulations of intermediate filaments. In some retracted neurons, bundles of neurofilaments were very densely interwoven and filled the entire perikaryon except for a narrow peripheral rim of granular cytoplasm. Focal aggregates of membranous vesicles among the condensed neurofilaments corresponded in location and size to some of the eosinophilic cytoplasmic inclusions seen with the light microscope. Such inclusions contained dense bodies, degenerating mitochondria, and membrane vesicles.¹⁸ Granular ribosomal-like clusters also produced cytoplasmic inclusions. Less common inclusions, occurring at the margin of the perikaryon, consisted of finely granular material within distended cisternae of rER. Filamentous accumulations extended into the dendritic stems and also appeared in maloriented arrays within proximal axonal swellings. Some axonal spheroids found in the ventral horns and traversing the ventral funiculus contained masses of mitochondria and membranous bodies in addition to condensed filaments. Hirano bodies (actin-containing, eosinophilic, rod-like intracytoplasmic neuronal inclusions that occur in human patients with ALS and other neurodegenerative diseases) were found occasionally in axons within the ventral horn (Fig. 5-69, B); some fibers in this area were distended by polyglucosan bodies, probably the result of advanced age.

Electron microscopic study of the ventral roots disclosed atrophic myelinated axons that had not been discerned with the light microscope. Wallerian-type degeneration was the most frequent change in both the ventral roots and peripheral nerves. Sites of axon degeneration were marked by persisting Schwann cell basal laminae, which often contained ovoids of degenerated myelin, proliferated Schwann cells, and invading macrophages. Some Schwann cells were more compactly arranged in typical B  ngner's bands. Evidence of axonal regeneration was only rarely encountered in the form of clusters of regenerating axons.

The progressive weakness and wasting in these horses and many of the underlying degenerative changes in the motor neurons (i.e., ribosomal loss, ghost cell formation, perikaryal shrinkage, neuronophagia, glial replacement, and ventral root axon degeneration) were more rapidly evolving but nevertheless very similar to those observed in humans with motor neuron disease or ALS.¹⁹⁻²² Moreover, the perikaryal and axon accumulations of neurofilaments resembled those commonly recorded in ALS.²³⁻²⁵ Comparison of this equine disease and sporadic ALS grows somewhat tenuous, however, when the pyramidal systems are considered. In contrast to humans, the equine pyramidal or corticospinal system is poorly developed, and bilateral motor cortex ablations have produced no clinical deficits. Because the pyramidal system in the horse is vestigial and because it was not severely or consistently affected, it may be more appropriate to compare this equine disorder to progressive muscular atrophy, a variant of the ALS complex in which spinal motor neuron degeneration occurs exclusive of pyramidal involvement.

The cause of this equine motor neuron disease is unknown. In exploring etiological possibilities, however, it would seem worthwhile to include the proffered causes of ALS, such as heavy metal poisonings, plant-derived intoxications, mineral deficiencies, endocrine dysfunction, viral infections, autoimmune disorders, inherited defect or predisposition, trauma, accelerated aging, and lack of growth factors.^{1,22,26} In preliminary investigations, Tom Divers at Cornell has found that affected horses have markedly depressed blood levels of vitamin E. This finding, together with recent evidence implicating the superoxide dismutase gene in the familial form of ALS, suggests a role for free radicals in producing neuronal injury. Studies on this spontaneous neurodegenerative disease of horses possibly may yield important clues on the pathogenesis of human motor neuron disease.

Unusual LMN disease has been observed in two older cats referred to us from Oregon by F. Clarke Berryman. Both cats were euthanized after a long course of progressive weakness. In one animal, signs were present for 3 years; in the other, they existed for 1 year. Both cats had a crouched gait, marked muscle atrophy, and fasciculations in the tongue.

Microscopic examination of cervical, thoracic, and lumbar spinal cord segments revealed profound loss of motor neurons in the ventral horns. The extensive loss of motor axons in the ventral roots was responsible for faint myelin staining with Luxol fast blue. The loss of motor neurons was associated with mild astrogliosis and large numbers of macrophages in the ventral horns. Although very few motor cytons had survived in these specimens, swollen axons were found occasionally in the ventral horns. These spheroids were distended with filamentous accumulations, and their myelin sheaths were either greatly attenuated or absent.

Study of the brain stem was limited to a few sections. Nevertheless, vacuolated cell bodies were identified in the oculomotor nucleus, and the facial nucleus contained ghost cells.

Because the clinicopathological information on these two older cats with lower motor disease is fragmentary, it is clearly speculative to suggest that the two cats suffered from the same disorder or that the disorder was acquired rather than inherited.

Hartley and Clarkson²⁷ have briefly recorded an epidemic of motor neuron disease that produced acute flaccid tetraplegia in 1- to 2-month-old goat kids. Pathological changes were most severe in the spinal cord and ranged from swelling and pallor to shrinkage with eosinophilia of somatic motor neurons. Wallerian degeneration was found in the brain stem, spinal cord funicular white matter, and ventral spinal roots and nerves. The cause was not established but a food-borne toxin was suspected; with a change in the diet, the syndrome disappeared.

A novel LMN disease has been described in lymphoma-prone wild mice from southern California.²⁸ This fatal neurological disease is associated with a unique exogenous ret-

rovirus (murine leukemia virus, MuLV) found only in these mice; paralytic disease can be induced by inoculating susceptible mice with MuLV.²⁹ After 1 year of age, mice develop pelvic limb paralysis resulting from motor neuron loss. Pathological changes are spongiform and are focused in the lumbosacral spinal cord, both gray and white matter. More cranial portions of the spinal cord and brain stem motor nuclei are more mildly affected. There is remarkable cytoplasmic vacuolation of neurons and of astrocytes and oligodendrocytes.³⁰ Motor neuron loss is accompanied by a reactive gliosis, but as infected mice are tolerant to the virus, inflammatory lymphoplasmacytic responses are lacking.²⁸ Budding of the C-type particles is seen within cisternae in ventral horn motor neurons. Tissue damage may be mediated directly by the virus (and its products) or indirectly, via vascular injury or subsequent to microglial infection.³¹ Lymphoma occurs also with high prevalence in this mouse population. Murine mutants with inherited motor neuron disorders include the **wobbler mouse**³² and the **wasted mice syndrome**.³³

Neurofibrillary accumulation

We can now review the **LMN diseases characterized by neurofibrillary accumulation**. Neurofilaments are the intermediate filaments characteristic of neurons, and underlying this group of diseases are disorders of neurofilament synthesis, catabolism, or transport. Sporadic examples have been described in the **dog**,³⁴ **cat**,³⁵ and **zebra foal siblings**.³⁶ Where it has been possible to study several animals, an hereditary basis has been suspected. The clinical scenario is fairly stereotyped, namely, an early onset of weakness and paresis, progressing to tetraplegia at a few weeks of age. At this stage, animals are recumbent, hypotonic, and hyporeflexic. There is neurogenic muscle atrophy, but nociception is usually retained. Death results from progressive inanition and respiratory complications.

Microscopic examination shows that filamentous degeneration is marked in the spinal motor neurons. Degenerative changes usually have also been found in the motor nuclei of the cranial nerves and sometimes in the red nucleus and brain stem reticular nuclei as well. Advanced changes are marked by perikaryon loss, glial nodules, and neuronophagia. Surviving cell bodies are often enlarged and chromatolytic. The pattern of chromatolysis is described variously as peripheral, central, or complete. On silver preparations, the chromatolytic areas of the swollen cell bodies are argyrophilic and present a whorled appearance. Electron microscopy reveals that these areas contain massive accumulations of 10-nm filaments. These neurofilaments are aggregated in interlacing bundles that appear to marginate diminished amounts of rER. Apart from the spinal muscular atrophy in Brittany Spaniels, large neurofilamentous spheroids in the proximal motor axons are not a salient finding in most of these animal diseases. The degeneration and loss of motor perikarya are associated with Wallerian degeneration in the ventral roots and peripheral nerves.

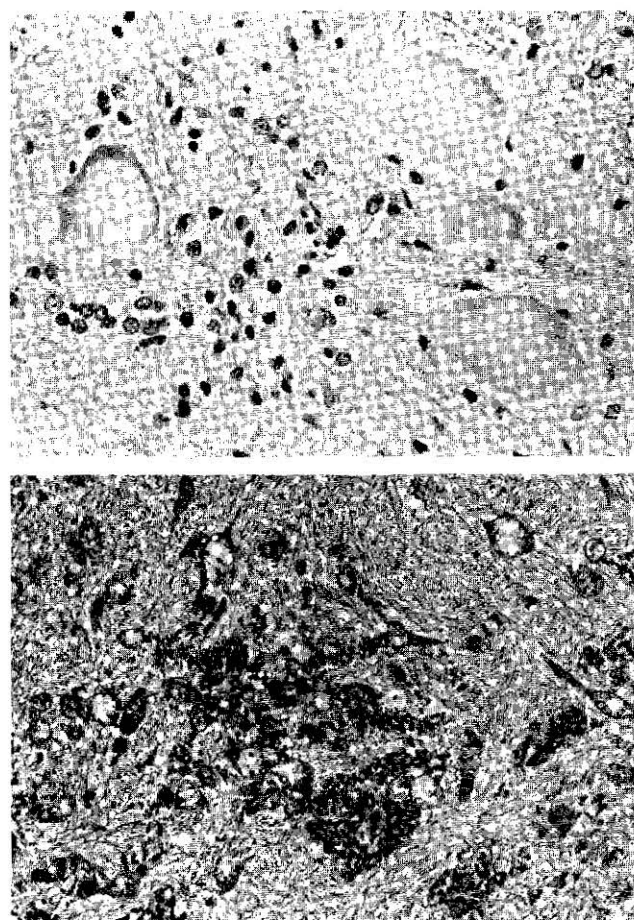


Fig. 5-70. Motor neuron disease, rabbit. **A**, Pale, distended neurons, spinal cord ventral horn. (H&E, $\times 350$.) **B**, Tangled arrays of neurofilaments fill perikaryon. A few aggregates of ribosomes and mitochondria are seen. ($\times 11,500$.)

Spontaneous LMN disease was reported in 6- to 8-week-old **rabbits**.³⁷ All were sired by a common male, implicating an hereditary basis for the condition, which affected both males and females. Motor deficits progressed to tetraplegia in 3 to 4 weeks. At necropsy, there was severe muscle wasting. Degeneration occurred in neurons of the lateral sector of the ventral gray horns, most severe in the lumbar and cervical intumescences; some cranial nerve nuclei were likewise affected. Pathological changes in neurons began with swelling of the perikaryon, margination of the nucleus, and disintegration of Nissl bodies (Fig. 5-70, A). Some neurons were lost, their demise recorded by an astrocytic gliosis. Wallerian degeneration occurred in the spinal cord white matter (lateral and ventral funiculi), the ventral spinal roots and nerves, and cranial nerves. Muscle fibers showed type II atrophy with small and angular fibers and mild type I hypertrophy. Ultrastructural examinations revealed perikarya of motor neurons that were swollen with masses of neurofilaments that entrapped or displaced normal organelles (Fig. 5-70, B). Filaments were approximately 10 nm

in diameter and straight, with short side arms. They filled the cell body and the proximal segments of dendrites and axons. Trapped within the bundles of neurofilaments were many mitochondria, vesicles, and lysosomal dense bodies. Endoplasmic reticulum and their ribosomes were disrupted and displaced to the cell margin.

Hereditary canine spinal muscular atrophy³⁸ is inherited in **Brittany Spaniels** as an autosomal dominant trait.³⁹ Animals homozygous for the trait develop an accelerated LMN disease, whereas heterozygotes have either an intermediate or chronic form of the disease with later onset and slower progression of muscle weakness and wasting. The proximal musculature is affected earlier and more severely than the distal appendicular muscle.^{40,41} The extraocular and sphincter muscle functions are preserved, although tongue, masticatory, and facial muscles are affected. In the accelerated form, pups develop signs at 4 to 6 weeks and become severely tetraparetic by 4 months. The clinical course is similar to that observed in spinal muscular atrophy of infants or Werdnig-Hoffmann disease. The intermediate form is most common; signs appear at 4 to 12 months and tetraparesis eventuates by 3 years. This pattern resembles that found in juvenile spinal muscular atrophy or Kugelberg-Welander syndrome.⁴¹ The chronic form has been infrequent and results in milder weakness. In keeping with the clinical findings, electrical evidence of denervation (e.g., fibrillations and positive sharp waves) appears first in the proximal musculature.⁴⁰

The pathological changes that selectively involve motor neurons of the brain stem and spinal cord reflect impairment of slow axonal transport.⁴¹⁻⁴⁴ The effects of this impairment are most evident in animals with the accelerated form of the disease.⁴³ Diminished transport of neurofilaments leads to their increased prominence within chromatolytic perikarya and dendrites. The most marked accumulation of these 10-nm intermediate filaments, however, occurs in the proximal course of the motor axons. Here, large masses of mal-oriented neurofilaments form the ultrastructural basis for argyrophilic intraspinal spheroids that are commonly observed with the light microscope. The impaired transport of neurofilaments, which leads to spheroids in the axon proximally, also leads to a gradual atrophy of the axon distally. This distal reduction in axon diameter reflects a diminished renewal of the cytoskeletal elements due to defective transport.⁴⁵ In animals with the slower, intermediate form of the disease, there is greater loss of perikarya, fewer intraspinal spheroids, and glial bundle formation in the proximal ventral roots. Morphometric studies of dogs with the intermediate and chronic phenotypes revealed an increase in the numbers of ventral horn neurons, compared with controls, with a shift in the distribution toward the smaller perikarya.⁴⁶ Diameters of motor axons in ventral spinal roots were similarly altered,⁴⁷ and it was proposed that LMN changes may reflect both growth arrest and atrophy.

Canine inherited spinal muscular atrophy has also been

considered as a model for the study of amyotrophic lateral sclerosis in humans. The presence of large argentophilic spheroids near the perikarya of the spinal motor neurons is also regarded as highly characteristic of this human neurodegeneration.⁴⁸

A LMN disease with spinal muscular atrophy has been described in the **Rottweiler**.⁴⁹ Paresis of pelvic limbs at 4 weeks of age progressed to paraparesis by 6 weeks. Regurgitation of food due to megaesophagus is a feature of the severe form of this syndrome, as well as pronounced muscle atrophy and limb contracture. The pathological changes have been described and are classical,⁵⁰ involving spinal cord motor neurons and the oculomotor, trigeminal, and ambiguous nuclei. We have studied a 2-month-old Rottweiler puppy with milder LMN progressive signs but similar motor neuron degeneration. In addition, degeneration was observed in sensory neurons in spinal ganglia and vestibular, cochlear, and cerebellar nuclei.

Yorkshire pigs have been reported to develop a spontaneous LMN disease with neurofilament accumulation.⁵¹ Signs of neurological disorder begin at 5 weeks of age with pelvic limb paresis that progresses rapidly such that by 10 weeks affected piglets are recumbent. In keeping with a disorder of motor neurons, weakness is the most prominent sign, especially at the onset, and EMG studies of muscle reveal positive sharp waves and fibrillation potentials. Microscopically, there is degeneration and loss of motor neurons from the ventral gray horn of the spinal cord and the oculomotor, trigeminal, facial, hypoglossal, and red nuclei. In H&E-stained sections, affected cell bodies and their neurites are swollen and pale and have a central but condensed nucleus, a somewhat swirled nature to the cytoplasm, and a loss of peripheral Nissl bodies. Nuclear disintegration proceeds, and chromatolysis becomes diffuse, leaving only dusty remnants within the perikaryon. Some necrotic neurons, contracted and dark, undergo neuronophagia. Wallerian degeneration is found in the lateral and ventral funiculi of the spinal cord, brain stem, and peripheral nerves; muscle fibers are small and angular, consistent with denervation. The neurofilamentous accumulation can be demonstrated immunocytochemically (Fig. 5-71, A). Ultrastructurally, there is a progressive dissolution of the ribosomal aggregates and a distension of the soma, dendrites, and axon with masses of 10-nm intermediate filaments that displace other organelles. An hereditary basis for this disorder was suspected but could not be proven. A clinically and pathologically similar syndrome has been observed in **Hampshire pigs**.⁵²

In horned **Hereford cattle** in Canada, there is a unique motor neuron disease with neurofilament accumulation.⁵³ The mode of inheritance is not established. Within a few hours of birth, affected calves have generalized tremors, wobbly spastic gait, and difficulty in standing. They are hyperesthetic to tactile stimulation. Some succumb early; others transiently improve and subsequently deteriorate over

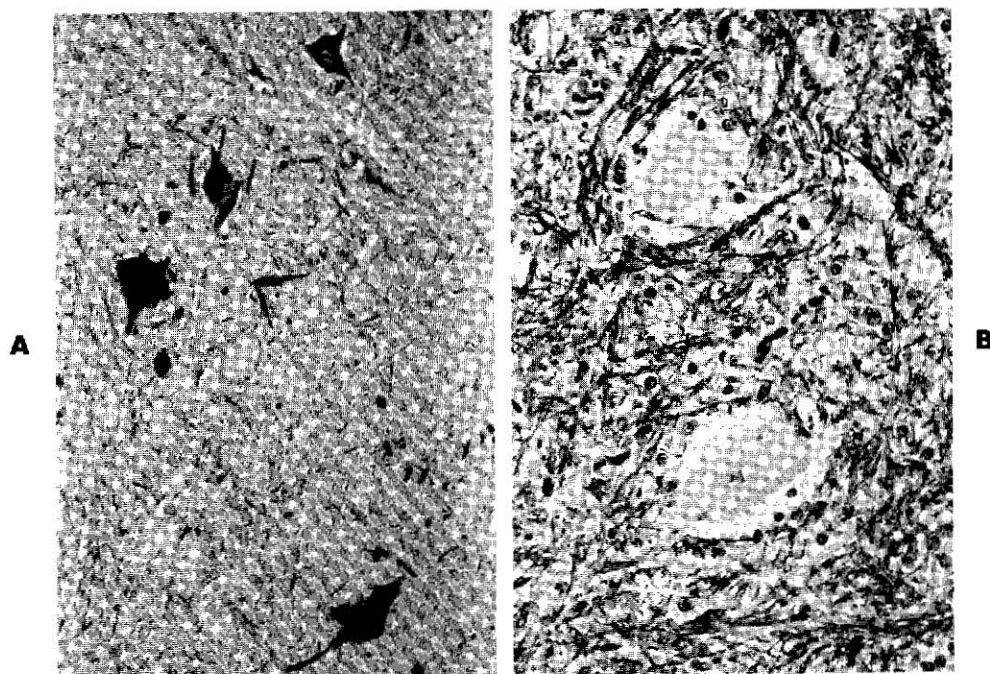


Fig. 5-71. Motor neuron disease. **A**, Pig. Neurofilament immunocytochemistry strongly labels motor neurons in the spinal cord. ($\times 140$.) **B**, Brown Swiss calf. Two fading ghosts: advanced motor neuron degeneration, spinal ventral horn. (Luxol fast blue, cresyl echt violet, $\times 350$.)

a course of several weeks. At necropsy, neurodegenerative changes were found in the CNS and PNS, including autonomic ganglia. There was swelling of the neuronal perikaryon, dendrites, and proximal axons with a fibrillar, acidophilic cytoplasm. Wallerian degeneration in ventral spinal roots was noted. Ultrastructural studies revealed massive accumulations of whorled 12-nm-diameter neurofilaments that segregated into clusters or displaced normal organelles.

A LMN disease in **brown Swiss calves** has been described.^{54,55} Of those whose sex was recorded, the majority were females. Affected calves became paraparetic between about 2 and 6 weeks of age, although some cases are congenital. Soon thereafter, many were recumbent and died, commonly with bronchopneumonia. Gross findings post-mortem were atrophy of appendicular muscles. Microscopically, there were swollen, chromatolytic somatic motor neurons in the spinal cord ventral gray horns and brain stem nuclei. Neuronal degeneration (Fig. 5-71, *B*) proceeded to neuronophagia, and glial foci marked the depleted horns. Spheroids were numerous in the spinal cord, while the ventral spinal roots showed Wallerian degeneration. Ultrastructurally, perikarya were packed with neurofilaments and abundant, swollen mitochondria. What is probably the same disorder was described in **red Danish calves** derived from American brown Swiss lineage.^{56,57}

References are on page 347.

NEUROAXONAL DYSTROPHY

The neuroaxonal dystrophies (NAD) are a group of inherited or acquired neurodegenerative disorders of humans and animals. The manner of inheritance, where known or suspected, is autosomal recessive. NAD also occurs in vitamin E deficiency, in delayed organophosphate poisoning and some other intoxications, in association with aging, and in the peripheral component of the autonomic nervous system of the diabetic rat.¹ In **humans**, the inherited form of NAD usually presents by 2 years of age with diminished activity, progressive weakness, hypotonia, and reduced tendon reflexes. As well as this infantile form, neonatal, late infantile, and juvenile patterns are recognized.^{2,3} In some patients, the course is marked by seizures. The characteristic pathological findings are disseminated axonal swellings (spheroids) in preterminal portions of axons and in synaptic terminals. In humans, involvement of the peripheral nervous system including the autonomic component is recognized, and the diagnosis can be made from skin, conjunctival, and rectal biopsies.^{4,5}

The clinical⁶ and pathological⁷ aspects of NAD in **Rottweiler dogs** have been described. Typically, affected dogs are clumsy with a mild gait abnormality by 1 year of age, although an earlier onset has been recorded.⁸ Forelimb hypermetria is an early sign. This deficit progresses over 1 to 2 years to more obvious cerebellar ataxia with hypermetria,

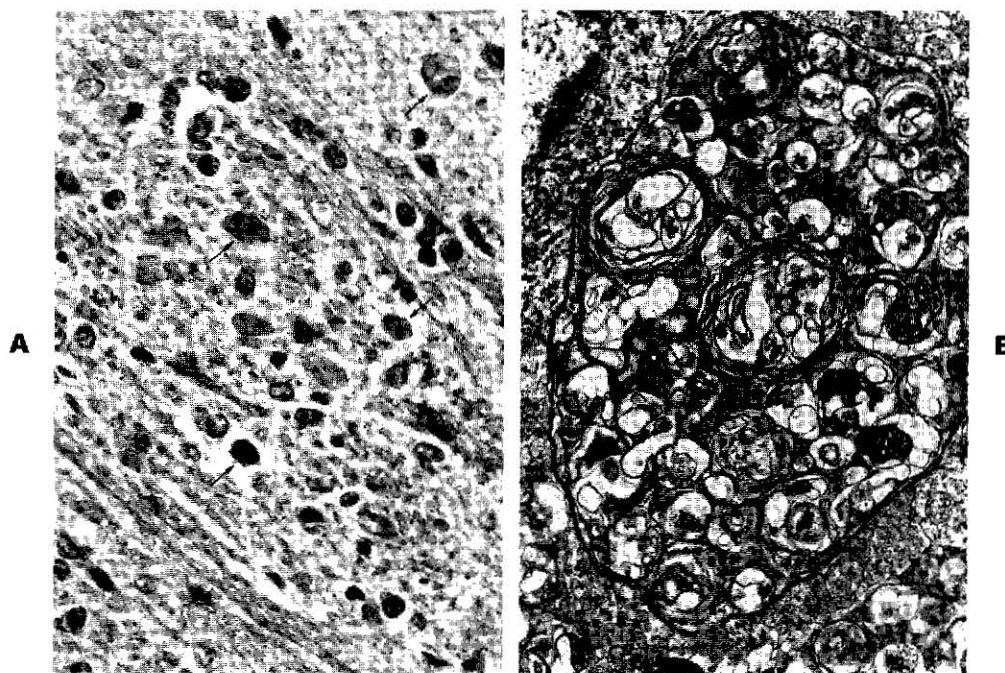


Fig. 5-72. Neuroaxonal dystrophy. **A**, Lamb. Axonal swellings (*arrows*) in spinal cord gray matter. (H&E, $\times 560$.) **B**, Dog. Membranous aggregates distend axon. ($\times 12,500$.)

intentional head tremor, and abnormal nystagmus. Pathological changes are progressive, mirroring the clinical signs. The brain is grossly normal or shows mild cerebellar atrophy. Microscopically, there are numerous axonal swellings distributed throughout the gray matter, topographically related primarily but not exclusively to sensory axon terminals; they particularly involve the dorsal horn of the spinal cord; vestibular, gracile, and cuneate nuclei; lateral and medial geniculate nuclei; and the nucleus thoracicus. Spheroids are ovoid, lightly to densely eosinophilic, and homogeneous or granular; some have a filamentous, argyrophilic core. There is mild loss of Purkinje cells and granule cell neurons from the cerebellar cortex. Ultrastructural studies reveal that the distended axons harbor a variable admixture of tubulovesicular arrays, profiles of smooth membranes, vesicles, and neurofilaments. Myelin sheaths over the dystrophic axons are attenuated or lost. The accumulation of organelles in axonal terminals suggests a disorder of "turn around" or retrograde transport, based on studies of labeled proteins in chronically induced neuropathies.

Blakemore and Palmer⁹ have recorded a strange axonal disorder in two **Chihuahua** puppies. Spheroids were remarkable for their predominance in white matter and for their content of membranous bodies with a myelin-like component. In **Collie sheep dogs** in New Zealand and Australia, NAD is reported,¹⁰ mainly affecting the cerebellar white matter. An inherited basis for the disorder is suspected. We have recently studied a 9-week-old **Jack Russell Terrier** with progressive signs of a diffuse brain disturbance. Both lateral ventricles were extensively dilated and neuroaxonal

dystrophy was widespread throughout the brain stem nuclei, especially in medullary proprioceptive and vestibular nuclei and in diencephalic nuclei. Spheroids also occurred throughout the spinal cord gray matter, with a few in the dorsal funiculi.

Duncan and Griffiths have described the syndrome of giant axonal neuropathy in the **Alsation dog**.¹¹ Axonopathic changes are found in both the CNS¹² and the PNS.¹³ These neurofilament-rich axonal swellings are larger and involve longer stretches of the axon than do the focal enlargements characteristic of NAD. Giant axonal neuropathy is discussed in Chapter 7.

Hereditary NAD was reported in the **cat** in association with coat color abnormality.¹⁴ Symptomatic kittens showed head shaking and bobbing, were ataxic, and appeared to have impaired vision. At necropsy, the cerebellar vermis was small. There was microscopic evidence of Purkinje and granule neuron cell loss. Axonal spheroids were most abundant in the olivary and lateral cuneate nuclei and brain stem tegmentum. Some were remarkably ballooned with a finely granular homogeneous quality and occasionally a dark center. Ultrastructurally, these contain membrane-bound vacuoles, mitochondria, dense bodies, and filaments. A further report of feline NAD in 4 related animals has been published.^{14a}

Neuroaxonal dystrophy was observed in purebred **Suffolk sheep**.¹⁵ Between 1.5 and 5 months of age, these lambs developed a progressive ataxia, distinguished by an unsteady, stiff, and swaying gait, worse in the pelvic than thoracic limbs. With time, affected lambs became recum-

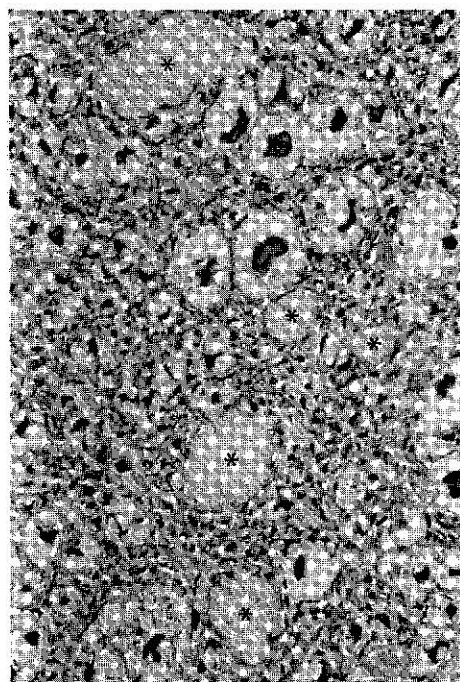


Fig. 5-73. Ovine segmental axonopathy. Pale, swollen axons (*asterisks*) in spinal cord funiculus. (Luxol fast blue-silver, $\times 560$.)

bent. Pathological changes, which were microscopic, consisted of numerous focal axonal swellings (Fig. 5-72, A) in gray matter and immediately adjacent white matter. Neuronal cell body changes, tract degeneration, demyelination, and gliosis were lacking. Some spheroids apparently underwent lysis, leaving an empty vacuole in the neuropil. Spheroids were most numerous in spinal cord gray matter (dorsal and intermediate gray horns), gracilic, medial, and lateral cuneate nuclei, and olivary, lateral reticular, and vestibular nuclei. The distribution is similar to that in the Rotweiler dog and primarily involves afferent systems involved in proprioception. Distinct from this syndrome in Suffolks is a disorder described as a segmental axonopathy in Australian **Merino sheep**.¹⁶ Affected animals, 1 to 4 years of age, showed progressive pelvic limb paresis. Ballooned axonal spheroids were found in large white matter tracts of the CNS (Fig. 5-73). In contrast, Harper and Morton described typical NAD in 4- to 7-month-old **Merino lambs** in which the spheroids were most prominent in the gray matter of the brain stem and spinal cord and rarely occurred in white matter.¹⁷

Neuroaxonal dystrophy has been observed in some **rabbits** that are genetically deficient in the sixth component of complement.¹⁸ Clinical signs begin with pelvic limb weakness at about 4 months of age. Some affected rabbits were paraplegic and had succumbed by 6 months. Pathological study showed widespread spheroids, mainly in the gray matter of the spinal cord and brain stem. An extensive peripheral neuropathy was also present, apparently account-

ing for the clinical presentation. The NAD is believed to be inherited as an autosomal recessive trait. In a kindred of Brittany Spaniel dogs with hereditary spinal muscular atrophy (motor neuron disease), deficiency of the third component of complement has been observed.¹⁹

The syndrome of **equine degenerative myeloencephalopathy (EDM)** has features of NAD. Axonal spheroids, however, occur focally in the face of extensive Wallerian degeneration of long tracts in the spinal cord. We have chosen to discuss EDM elsewhere and, with it, a disease that may be a form of EDM in the **Morgan horse** that has been reported as NAD of the lateral (accessory) cuneate nucleus in horses.^{20,21} For a true NAD to affect only a single nucleus would be exceptional. Two sibling **Hafflinger horses** with NAD have been reported from Germany.²² Both animals developed mild pelvic limb ataxia at 4 months of age. Hindlimb deficits worsened, and a mild thoracic limb gait disturbance developed. At necropsy, variably sized eosinophilic axonal spheroids, compartmentalized vacuoles, and macrophages containing a yellow-brown pigment were found in several nuclei, including the lateral and medial cuneate and gracilic nuclei and the nucleus of the solitary tract, nucleus thoracicus, nucleus centrobasis, and nucleus intermediomedialis. Both animals had low serum levels of α - and γ -tocopherol.

Focal axonal swellings within the CNS are prominent in some lysosomal storage diseases (discussed earlier in this chapter), and deranged axonal function may contribute to the clinical deficits in these diseases.²³

References are on page 348.

EQUINE DEGENERATIVE MYELOENCEPHALOPATHY

Of several syndromes that cause neurological disease in the horse,¹ equine degenerative myeloencephalopathy (EDM) is the most common in our hospital population. First described in the horse in 1977,² EDM was so named to emphasize the diffuse nature of the degenerative changes in the spinal cord; involvement of the brain is focal and limited to the caudal brain stem. This syndrome occurs in many pure and mixed breeds of horses such as Arabians, Appaloosas, Thoroughbreds, Standardbreds, and Morgans. Sometimes clusters of cases occur that can be taken to implicate a familial tendency or a local environmental influence. A clinically similar disease in the Morgan breed has been designated neuroaxonal dystrophy,^{3,4} and syndromes clinically and pathologically similar if not identical to EDM have been described in the zebra (*Equus burchelli*)⁵ and the Mongolian wild horse (*Equus przewalskii*).⁶

This syndrome has been recognized in the United States,^{2,7-9} Canada,¹⁰ Australia,¹¹ and England.¹² The onset of clinical disorder is typically insidious, usually within the first 2 years of life and often by 6 months of age. Nonetheless, approximately 20% of cases are first observed with clinical signs when the horses are 28 months of age or older.⁷

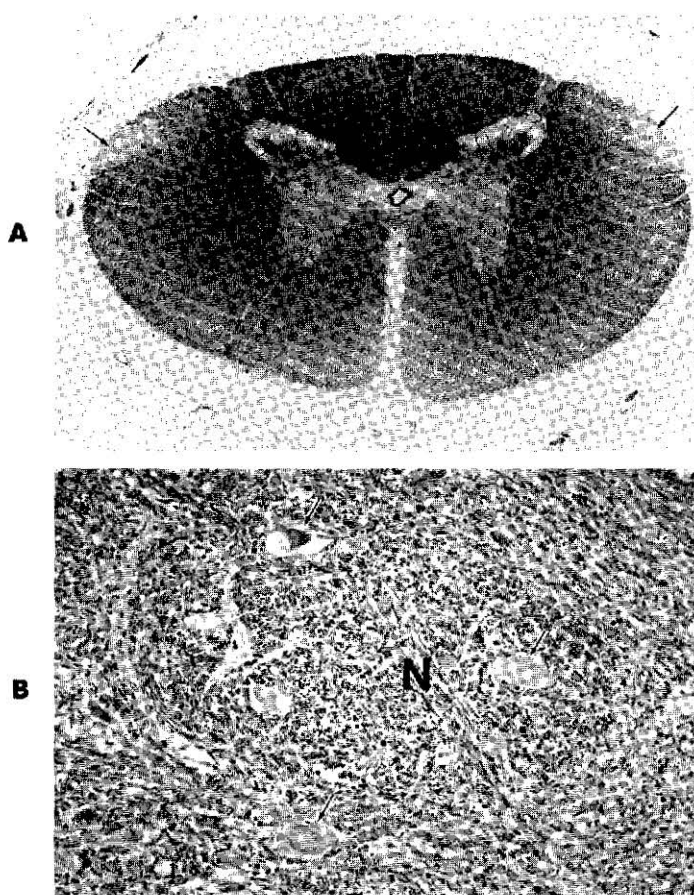


Fig. 5-74. Equine degenerative myeloencephalopathy. **A**, Thoracic spinal cord. Pronounced degeneration in the dorsal spinocerebellar tracts (*arrows*). More widespread and milder degeneration in peripheral area of lateral and ventral funiculi, (Luxol fast blue, cresyl echt violet, $\times 9$.) **B**, Nucleus (*N*) of the dorsal spinocerebellar tract. Spheroids (*arrows*). (Neurofilament immunocytochemistry, $\times 180$.)

These signs reflect the diffuse degeneration that is present throughout the spinal cord and as such appears in all four limbs, usually symmetrically. All limbs may be equally affected, or pelvic limb deficits may be more pronounced. The gait is spastic with a prolonged stride in the forelimbs and a basewide stance and gait in the pelvic limbs. The hooves of the pelvic limb may be scuffed, and tight circling produces delays in protraction, overabduction, and crossing the limbs. Severely affected animals may sway extensively and fall if turned too quickly. Deficits reflect a combination of general proprioceptive and upper motor neuron pathway lesions. The clinical course is usually slowly progressive over many weeks or months and after some time may plateau. The progressive degenerative changes and scarring are not compatible with recovery.

Pathological changes are microscopic, are diffuse in all segments of the spinal cord, and involve white and gray matter. Myelinated fibers in the dorsal, lateral, and ventral funiculi are all affected, although the dorsal columns are most mildly changed. Degenerative changes are most pro-

nounced in the dorsal spinocerebellar tracts of the lateral funiculus (Fig. 5-74, A) and within the sulcomarginal tracts in the ventral funiculus. In some cases, degeneration of peripheral (subpial) fibers involves the entire circumferential length of the lateral and ventral funiculi, or small patches of degenerate fibers may be found in this distribution. Lesions at any spinal cord level involve both ascending pathways in the lateral funiculus, which arise in nucleus thoracicus, and the predominantly descending fibers in the ventral funiculus, which arise presumably in brain stem nuclei. The changes are a progressive fragmentation of axons and ballooning of ensheathing myelin, forming chains of digestion chambers that are best visualized in longitudinal sections of the spinal cord. Macrophages attend to the axo-myelinic debris and a pronounced reactive astrocytosis, triggered by the myelin breakdown, dissects between surviving myelinated fibers. In H&E-stained transverse sections of spinal cord, the myelin-depleted astroglial areas produce bilaterally symmetrical areas of pallor that can be readily identified at low magnification; myelin stains accentuate this

pattern. In examining cases of EDM, it is possible to predict the nature of the clinical course from the character of the spinal cord changes; horses with a short course show extensive, active vacuolar degeneration of myelinated tracts, whereas chronic, stable cases are marked by extensive astrogliosis and lesser evidence of ongoing myelin breakdown. Fiber degeneration is most severe in the thoracic spinal cord, and here it is accompanied by neuroaxonal degeneration in nucleus thoracicus (Fig. 5-74, *B*). There are occasional degenerate neuronal cell bodies, swollen acidophilic axons (spheroids), and a yellow-brown granular pigment in the neuropil or within macrophages. Some spheroids are found outside the nucleus thoracicus, in the base of the dorsal horn, or in the intermediolateral columns. Similar and usually more pronounced axonal spheroid formation afflicts the medial and lateral (accessory) cuneate nuclei in the caudal medulla. Typically here, the larger spheroids undergo a vacuolar change (sometimes multiloculated), giving the nucleus, from low-power appraisal, a spongy appearance. Neuroaxonal degenerative changes are found inconsistently in other nuclei such as the olives, reticular formation, and vestibular nuclei.² Mild degenerative changes may be found in dorsal spinal rootlets.

What is probably EDM in **zebras**⁵ affected 8 of 17 foals between 4 and 6 months of age. Signs of an ataxic gait began in the pelvic limbs and worsened such that they were severely ataxic at 1 to 2 years of age. Lesions were as in the horse. What has been designated neuroaxonal dystrophy in Morgan horses^{3,4} is clinically very similar to EDM. Apart from one animal, significant degenerative changes were identified only in the lateral (accessory) cuneate nucleus. As Beech commented,³ these lesions cannot account for the predominantly pelvic limb ataxia that she observed because the lateral cuneate nucleus receives primary sensory projections from the neck and forelimb. Our suspicion is that these horses have subtle degenerative changes in the spinal cord. We have observed young Morgans with slowly progressive signs involving all four limbs and the typical lesions of EDM.

The etiology of EDM remains unknown, but several clues are emerging; it must be kept in mind that this may be more than one disease. Clusters of cases, sometimes progeny of a single stallion, hint strongly at a genetic influence, and a familial predisposition has been proposed.⁸ However, we are also aware of the scenario wherein a stallion has sired multiple progeny that have been raised in different environments and EDM has been observed only in his offspring on one farm. The pattern of neuronal fiber degeneration is reminiscent of the encephalomyelopathy in copper deficiency of lambs, goats, and deer. Initial studies in 1978¹³ and a more recent evaluation of liver and plasma copper levels in EDM¹⁴ have failed to associate this condition with low copper status. Delayed organophosphate poisoning can produce pathologically similar changes, and occasional overenthusiastic anthelmintic treatment of horses (with or-

ganophosphate compounds) may produce sporadic cases of a degenerative myeloencephalopathy. A case-control study of EDM, employing a questionnaire that contained hundreds of data items, has been published.⁷ The risk of developing the disease was higher in foals that had been treated with insect repellents, exposed to wood preservatives, or frequently housed on dirt lots. The first two risk factors (at least) may implicate a neurotoxic basis for this disease. This study also showed a higher risk for EDM in foals from dams that had a previously affected foal.

Chronic vitamin E deficiency in humans, usually due to malabsorptive disorders, and induced hypovitaminosis E in rats and primates result in a neuroaxonal dystrophy with some spinal cord degeneration. Mayhew and colleagues⁸ have shown that prophylactic administration of vitamin E significantly diminished the incidence of EDM on two farms. Although another study failed to demonstrate lower serum vitamin E levels at the time of clinical diagnosis,¹⁵ lower levels were noted in the youngest affected horses (under 12 months of age). This is significant, as Blythe and associates⁹ have shown that foals destined to develop EDM have subnormal α -tocopherol levels between 6 weeks and 10 months of age and so perhaps could be normal at the time of clinical diagnosis. Furthermore, vitamin E status in horses is more securely evaluated from several, rather than single, serum samples.¹⁶ The role of vitamin E gains credence from what is probably EDM in Mongolian wild horses that had low plasma α -tocopherol levels.⁶ The effects of hypovitaminosis E in domestic animals are many and varied and include degeneration of skeletal and cardiac muscle, steatitis, hepatocellular necrosis, and, in the chicken, encephalomalacia.¹⁷ The neuroaxonal dystrophy observed in nucleus thoracicus and the proprioceptive nuclei of the medulla in horses with EDM is also associated with aging. It has been proposed that vitamin E deficiency may cause premature aging,¹⁸ vitamin E acting as an antioxidant and preventing peroxidation of cell membranes. Consistent with a vitamin E deficiency in EDM is our ultrastructural observation of prominent lipopigment deposits in spinal capillary and venule endothelia.

References are on page 349.

DEGENERATIVE MYELOPATHY OF OLD ANIMALS

A chronic progressive leukomyelopathy occurs in aged **German Shepherds** and other predominantly large dog breeds. This syndrome has been referred to as progressive paraparesis in German Shepherd dogs, German Shepherd dog myelopathy,^{1,2} and chronic degenerative radiculomyelopathy.³ Affected dogs, typically older than 5 years of age, present with a history of slowly progressive paraparesis and ataxia of the pelvic limbs. Important clinical clues are the insidious onset, a prolonged course, and a sparing of the thoracic limbs, despite pathological involvement of the cervical spinal cord. Loss of strength and wasting of the

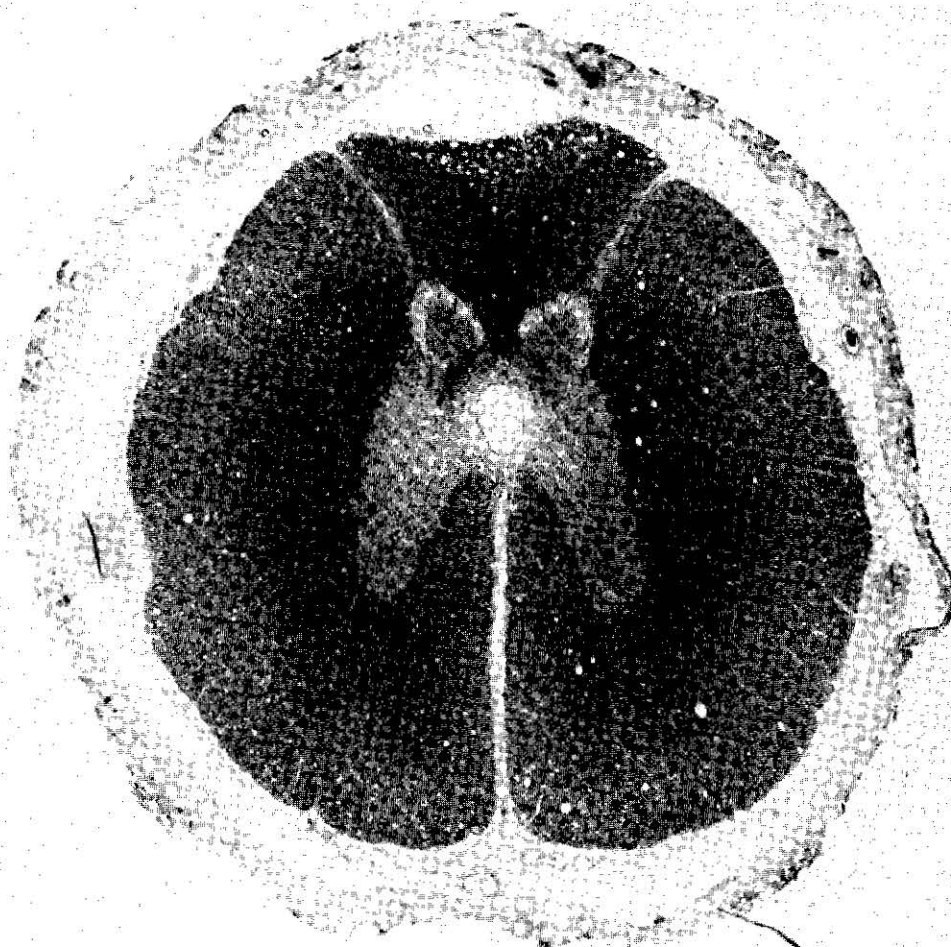


Fig. 5-75. German Shepherd myelopathy. Fine myelin vacuolation randomly disposed in all funiculi of the thoracic spinal cord. (Luxol fast blue, cresyl echt violet, $\times 20$.)

pelvic limbs is slowly progressive. During gait, the animals crouch in the pelvic limbs, sway from side to side, cross the limbs, and drag the toes. Patellar reflexes are usually brisk, but in approximately 15% of cases are depressed or absent. The CSF is usually normal.

At necropsy, a diffuse myelopathy is found to affect all funiculi throughout the length of the spinal cord; the brain stem is not involved.¹ As in other myelopathies (Afghan hound myelopathy, hound ataxia, equine degenerative myeloencephalopathy), the thoracic segments bear the brunt of the injury.² Lesions are bilateral but not necessarily symmetrical, and this may be reflected clinically as unequal deficits between left and right pelvic limbs. Histological changes are degenerative and involve myelinated axons. There is myelin ballooning, disruption, and phagocytosis by myelophages while axons fragment and disappear. Degenerative changes involve superficial (subpial) and deep fibers in both ascending and descending pathways (Fig. 5-75). There is no selective tract involvement, and lesions are said to be discontinuous.² The distribution of this lesion is best appreciated in transverse sections of the spinal cord,

but the discrimination between myelin ellipsoids and artifactual vacuolation of myelin sheaths is most readily made in longitudinal sections. A mild to moderate astrocytosis accompanies these degenerative white matter changes. Griffiths and Duncan³ proposed a dying-back process to explain these lesions, but Braund and Vandeveld² argue that, as the greatest density of lesions is in the thoracic segment, this is inconsistent with a dying-back hypothesis. No significant gray matter lesion has been observed. Wallerian degeneration occurs in the femoral nerve of dogs that have lost their patellar reflex and perhaps in a milder form in others. Involvement of lumbar dorsal nerve roots was observed in some cases by Griffiths and Duncan,³ but is not consistent and may reflect a concurrent aging change in some animals. An age-related radiculopathy has been described in the dog by these authors.⁴

The ultrastructural pathology of this canine myelopathy has yet to be described and indeed may not advance our understanding of the disease. Little is known of its cause. A genetic basis in German Shepherds is presumed and perhaps is supported by the recent observation of a similar

myelopathy in two young (6- and 7-month-old) German Shepherd dogs.⁵ An hereditary basis gains credence with the publication of a similar myelopathy in a family of Siberian Husky dogs.⁶ Peripheral blood lymphocytes from affected German Shepherd dogs have depressed proliferative responses to thymus-dependent mitogens,⁷ apparently because of suppressor cell activity.⁸ The importance of these observations to the pathogenesis of this disease is yet to be elucidated. German Shepherd dogs can develop an enteropathy associated with bacterial overgrowth in the small intestine,⁹ and Williams and associates¹⁰ have suggested that malabsorption of some vitamins may follow bacterial overgrowth in the gut. Vitamin E deficiency has been associated with encephalomyelopathy in humans and perhaps the horse, and the Williams group¹⁰ found depressed levels of serum tocopherol (vitamin E) in seven German Shepherd dogs with degenerative myelopathy. Averill¹ looked without success for evidence of vitamin B₁₂ deficiency in his series. A role for an infectious agent may seem unlikely, but vacuolar myelopathy has been associated with human HIV infection¹¹ and a chronic progressive myelopathy with human T-cell lymphotropic virus Type 1 infection.^{12,13}

This degenerative myelopathy of the dog is only rarely observed in smaller breeds.¹⁴ A comparable myelopathy has been reported in a mature cat.¹⁵ Paraparesis has been associated with myeloradiculopathy in senescent rats.¹⁶ Affected animals are usually 2 years of age or older, and the incidence varies with rat strain. Affected rats become paraplegic and wasted in the pelvic limbs. Their spongy myelopathy is very similar to that of the aged dog, involving all funiculi but least severely the dorsal columns; cranial thoracic segments are most severely affected. An associated radiculopathy affects dorsal and ventral spinal roots with myelin ballooning, Wallerian degeneration, and axonal dystrophy. Ventral roots are more severely injured in thoracic divisions, whereas lumbosacral root involvement is equally severe in dorsal and ventral roots. An age-related radiculomyelopathy has been observed in neurologically normal rats, appearing between 18 and 20 months of age.¹⁷ Lesions are most severe in the ventral spinal roots and peripheral nerve. Axonal degeneration has been mapped in the spinal cord of the aging rat¹⁸ and found to involve gray and white matter.

References are on page 349.

HOUND ATAXIA

In the United Kingdom and Ireland, a chronic pelvic limb ataxia is recognized in **Harrier Hounds**, **Beagle Hounds**, and **Foxhounds** kept in packs for hunting.^{1,2} Affected dogs, of either sex, are adults of 2 to 7 years of age. Clinical signs are manifest as a gradual onset of ataxia and spastic paresis with a swaying gait in the pelvic limbs. Many affected dogs lack a cutaneous reflex caudal to the mid-thoracic region. Thoracic limbs and cranial nerves are normal. The condition appears to be progressive and may

account for considerable depletion of the hound pack.

No gross postmortem findings are present, except that the spinal cord may be slightly shrunken. Microscopic findings are of Wallerian degeneration affecting all funiculi, but mildest in the dorsal funiculus. All spinal cord segments are affected, perhaps thoracic the most severely (Fig. 5-76). Changes consist of severe myelin ballooning with intramyelinic macrophages. Degeneration can be traced into the brain stem, but does not favor particular tracts in the spinal cord. Spinal gray matter, nerve roots, and spinal ganglia are, in most cases, normal. Electron microscopic findings are of depletion of myelinated fibers, prolific astrogliosis, and of thinly or abnormally myelinated axons in surviving fibers.²

The cause of this myelopathy is not known. The practice of feeding these hunting dogs largely on rumen (also known as paunch or tripe) with only occasional meat supplementation raises the possibility of a nutritional deficiency. Serum methionine levels in affected animals were lower than those of age-matched control dogs,² and this may be significant. Anatomically, this myelopathy closely resembles the degenerative myelopathy of mature German Shepherd and other large dog breeds.

References are on page 350.

ATAXIA AND MYELOPATHY IN TERRIER DOGS

A clinically and pathologically similar syndrome of progressive ataxia occurs in **Smooth Fox Terriers** in Sweden¹ and in **Jack Russell Terriers** in England.² Several Swedish Smooth Fox Terriers have been studied, and an autosomal recessive mode of inheritance established. Ataxia begins between 2 and 6 months of age. In both groups, deficits are more pronounced in the pelvic limbs, which are basewide, but the forelimbs are excessively hypermetric. The trunk sways and lurches in all directions because of the dysmetria and loss of balance. At a rapid pace, the gait has a dancing or prancing character. The head may show oscillating movements or intention tremor. The signs predominantly resemble a cerebellar disorder. The condition is not lethal, and affected dogs have been kept for many months.

Pathological findings are microscopic.^{2,3} There is a symmetrical, bilateral myelopathy, involving fibers in the dorsal part of the lateral funiculus and at the ventromedial sulcus of the ventral funiculus. These areas are slightly pallid and vacuolar in H&E preparations, with a mild, subpial astrogliosis. Myelin loss, secondary to Wallerian degeneration, is highlighted in myelin preparations. Involvement of the spinocerebellar tracts is most evident in the cervical spinal cord. In the Jack Russell Terrier, there are further marked vacuolar changes of myelin in the spinal roots, reminiscent of changes associated with aging in the dog.⁴ The dorsal nuclei of the trapezoid body are gliotic and depleted of myelinated fibers and contain spheroids (focal axonal swellings). The cochlear nuclei are less affected. Degenerative changes affect the trapezoid body and lateral lemniscus, but,

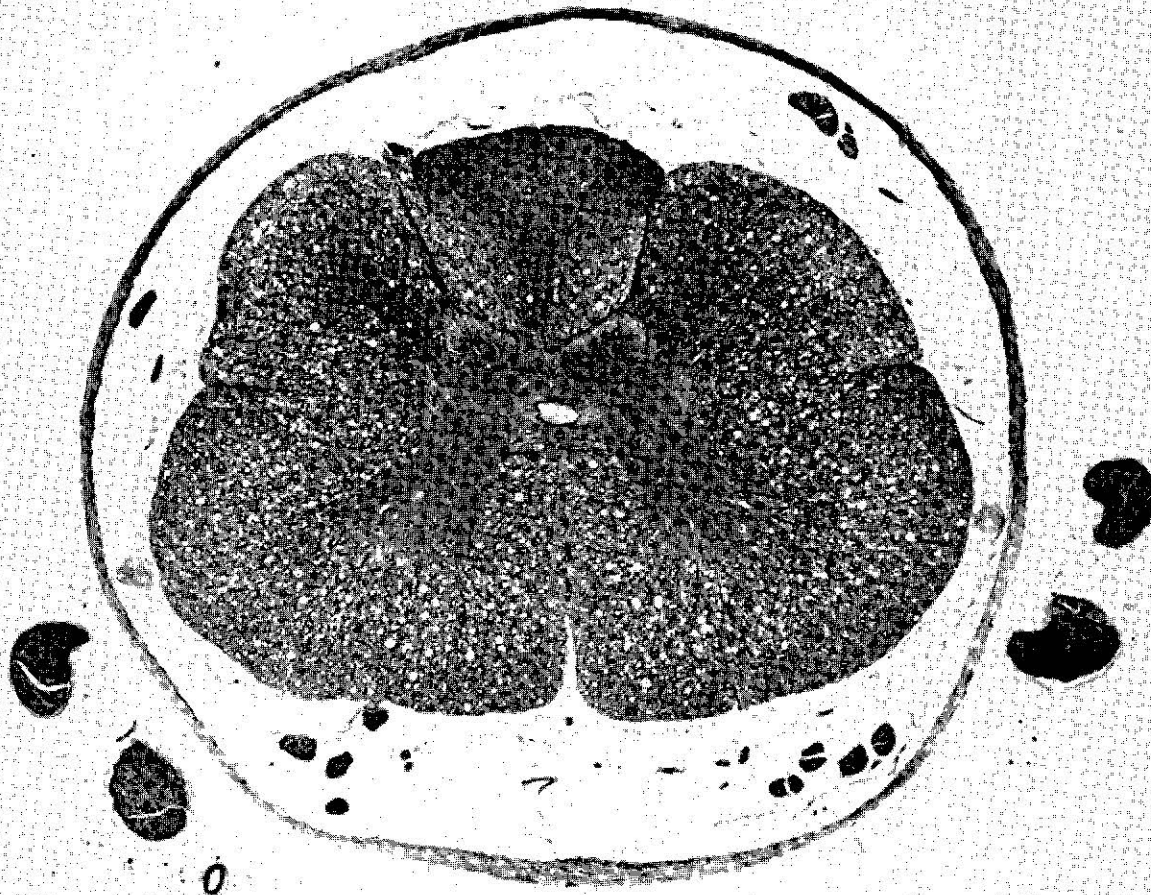


Fig. 5-76. Hound ataxia. Pronounced vacuolation in all funiculi of a thoracic spinal cord segment. (H&E, $\times 15$.)

despite this involvement of the central auditory pathway, loss of hearing was not recorded. Patchy Wallerian degeneration could be found throughout the CNS; peripheral nerves showed loss of myelinated fibers, axonal swellings, and fibrosis. The anatomical distribution of the microscopic lesions is not reflected in the major neurological signs, which are cerebellar.

References are on page 350.

NERVOUS SYSTEM DEGENERATION IN THE IBIZAN HOUND

A progressive neurological disorder of the Ibizan Hound dog was first recognized by W. Fenner at Ohio State University in 1981, about a decade before our first exposure to this condition. We have examined four dogs varying in age from 8 months to 2 years. All had a history of onset of a gait abnormality from about the time they first began to walk. Initially, ataxia was most pronounced in the pelvic limbs, but it progressed to the thoracic limbs. The gait was spastic and remarkably dysmetric, with overflexing and abduction. These jerky, awkward, misplaced strides and a loss

of balance produced a bobbing, bouncing type of gait. The trunk swayed excessively in any direction, and the dogs often fell. Patellar reflexes were absent, but muscle size was normal. No abnormal cranial nerve signs were observed. Some dogs also exhibited occasional partial or generalized seizures.

There are no gross lesions observed in the nervous system. On microscopic examination, there is a conspicuous bilaterally symmetrical degeneration of ascending and descending tracts involving all funiculi at all levels of the spinal cord (Fig. 5-77), but most extensively in the thoracic segments.¹ The lesions predominate in the lateral portion of the dorsal funiculus, the most superficial and dorsal portion of the lateral funiculus, and superficial portions of the ventral funiculus. Many large spheroids (up to 60 μm diameter) occur in the axons of the cochlear neurons in the trapezoid body. These stain with monoclonal antibody to neurofilaments, sometimes in a targetoid fashion with a paler center to the aggregate. The dorsal nucleus of the trapezoid body is gliotic. In the spinal roots and to a lesser degree in the named specific peripheral nerves, there are dilated myelin

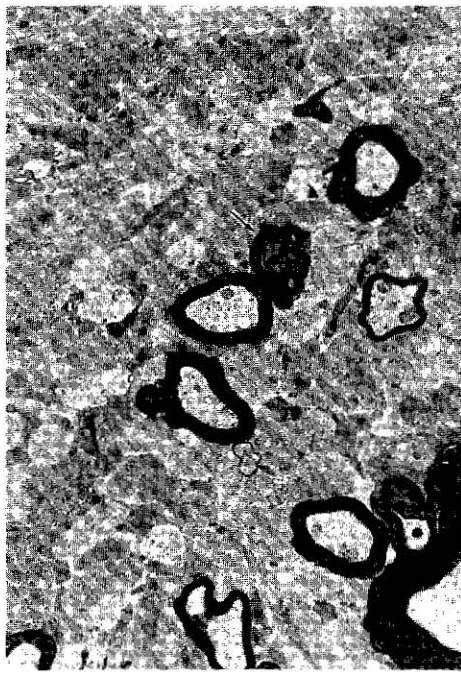


Fig. 5-77. Ibizan hound axonopathy. Paucity of myelinated axons, axon degeneration (arrow) and prolific astrocytosis. ($\times 5625$.)

sheaths containing intact axons and fewer chains of myelin ellipsoids with degenerate axons and macrophages. These lesions predominate in the ventral roots. Many peripheral nerve components contain excessive endoneurium. Neuronal cell body lesions were not observed to account for the long tract degeneration in the spinal cord. In summary, this is a diffuse nervous system degeneration with encephalomyelopathy and neuropathy predominantly affecting axons.

Pedigree analysis of affected litters of puppies supports an inheritance of an autosomal recessive genetic abnormality. The clinical signs and the character and distribution of the lesion have a close resemblance to the inherited disease reported in Smooth Fox Terriers in Sweden^{2,3} and in Jack Russell Terriers in England.⁴ The latter includes the unique involvement of the auditory system (trapezoid body and its nucleus).

References are on page 350.

LABRADOR RETRIEVER AXONOPATHY

Since 1988 a similar neurological disorder has been studied in 11 Labrador retriever puppies (8 males and 3 females) from a total of 36 puppies in 4 litters.¹ Two of these litters were from Nebraska and two from Ohio. The two litters in Ohio had the same sire, and the dams were related. In one litter the sire was bred to his dam. The Ohio and Nebraska litters have common ancestors 6 generations back.

The affected puppies have difficulty using their pelvic limbs at the time they first begin to walk and are slow to stand with them. As they develop the ability to stand and

walk, pelvic limbs initially are short-strided, adducted, and crouched; they tend to collapse and sway to the side, which often results in the puppy falling down. The forelimbs have better function but are stiff and mildly abducted (wide-based). These signs progress at a variable rate, and a degree of hypermetria appears in both the forelimbs and hindlimbs. The ataxic hindlimbs often swing wide to either side, which frequently causes them to fall. The forelimbs become progressively more spastic and abducted. As the hypermetria becomes more pronounced, the voluntary movements become more awkward with a jerky-dysmetric quality.

The signs progress at a variable rate. Most puppies become unable to get up and walk without assistance by 3 to 5 months of age. In the dogs studied after 3 months of age, the signs seem to progress slowly and then remain static. One dog was observed to 13.5 months of age with no significant change in the last few months.

Despite their inability to readily stand, the dogs still show tremendous desire to get up and run. They have difficulty righting themselves to a sternal posture from lateral recumbency. Nevertheless, after several efforts, they occasionally lurch to a standing position, take three or four very awkward, spastic, dysmetric strides before falling to either side. A head tremor occurs late in the course of the disease.

All ancillary studies are normal, including evaluation of cerebrospinal fluid.

All puppies had aplasia or hypoplasia of the corpus callosum. Two puppies had spina bifida at C7.

On microscopic examination, all dogs had an extensive bilaterally symmetrical degeneration of the spinal cord white matter that predominated in the superficial aspect of the dorsal part of each lateral funiculus where the spinocerebellar tracts course, the fasciculus gracilis of each dorsal funiculus, and, to a lesser extent, the ventral funiculus adjacent to the ventral median fissure. These symmetrical lesions were most extensive in the thoracic segments and decreased in intensity in the more caudal lumbar and sacral segments and in the more cranial cervical segments. The degeneration continued through the medulla, into the caudal cerebellar peduncles, and into the cerebellum. These lesions consisted of a complete to partial loss of axons and myelin with replacement by extensive astrogliosis (Fig. 5-78). Where the lesion was most extensive, there was no staining at all with the Luxol fast blue stain for myelin. Axonal stains (Holme's silver and monoclonal antibody for phosphorylated neurofilaments) confirmed the loss of axons in these lesions and, along with electron microscopy, showed a more extensive loss of the larger axons with preservation of smaller processes, especially in the partially affected deeper components of the lateral funiculi.

Another indication of the axonal degeneration was the presence of swollen axonal spheroids. These swollen structures were darkly stained with the axonal stains and in electron micrographs appeared to contain either disordered neurofilaments or collections of vesicles, mitochondria, and

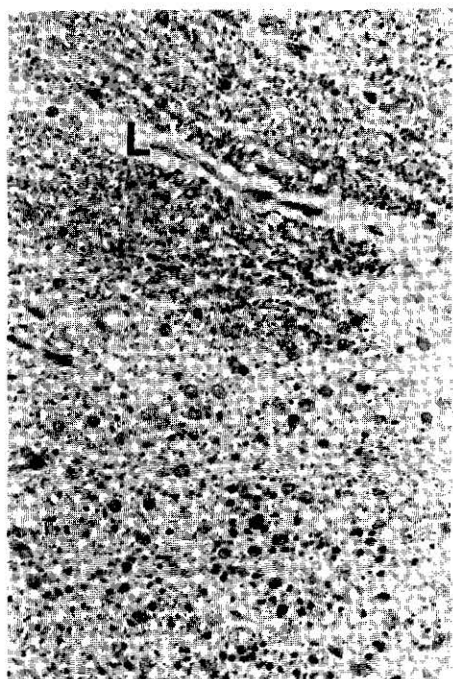


Fig. 5-78. Labrador retriever axonopathy. Spinal cord. Lissauer's tract (L) appears normal, but the adjacent dorsal spinocerebellar tract is depleted of axons and is astrocytic. (Neurofilament immunocytochemistry, $\times 350$.)

Golgi apparatus. In the spinal cord of the younger dogs, these spheroids were most common in the dorsal funiculus at all levels of the spinal cord. These were also prominent on the lateral surface of the medulla. A few were scattered in the cerebellar medulla and in the white matter of individual folia. In a few folia, there were numerous spheroids in the granular layer of neurons of the cerebellar cortex, some of which were continuous with the cell bodies of Purkinje neurons. A few spheroids were scattered in the transverse fibers of the pons and middle cerebellar peduncles, in the optic tracts, in the internal capsule, and in a few individual corona radiata of the cerebrum.

No cell body lesions were observed in spinal ganglia or any part of the spinal cord gray matter. In the medulla, cell body degeneration was extensive in each olivary nucleus. In this nucleus of dogs autopsied early in the course of the disease, there were numerous swollen chromatolytic cell bodies and fairly large spheroids. In the dog autopsied at 8 months, the olivary nucleus was nearly totally deficient in cell bodies, which were replaced with astrocytes. The monoclonal antibody stain for phosphorylated neurofilaments stained the contents of the cytoplasm of the swollen cell bodies as well as the spheroids. A few swollen degenerate cell bodies were seen in the vestibular nuclei and reticular formation.

This combination of a deficient development of the corpus callosum, an extensive symmetrical, predominantly spinal cord axonopathy, and a predominantly olivary neuronopathy has not been described in any other breed. It is

presently presumed that it is an inherited recessive abnormality.

References are on page 350.

MYELOPATHY IN KOOIKER DOGS

A progressive neurological disorder has been recognized in Dutch **Kooiker dogs** for over 30 years.¹ The trait appears to be inherited as an autosomal recessive disorder. Clinical signs begin in dogs of either sex between 3 and 12 months of age. Deficits first appear in the pelvic limbs and sometimes advance to involve the thoracic limbs also. There is an upper motor neuron paraparesis and an ataxia; spinal reflexes are exaggerated. Euthanasia is often performed by 12 months of age.

Postmortem findings are a diffuse leukomyelopathy that is evident grossly. In cross-sections of the spinal cord, the funiculi are dull and lack their normal white color. Microscopically, a diffuse necrotizing process is said to affect all funiculi, particularly at the cervical-thoracic junction. However, lesions are found in cervical, thoracic, and lumbar segments, most prominently in dorsal and ventral funiculi. Lesions vary from areas of myelin pallor to necrosis and cavitation with neovascularization and gitter cell formation. Wallerian degeneration is found below the lesions in descending tracts and above the lesions in ascending pathways, suggesting an axonopathic process within the primary areas of injury. Some lesions extend marginally into the ventral horns of the spinal cord. In a few dogs, degeneration has been observed in the trapezoid body and olivary nucleus.

The hereditary nature, age of onset, and topography of lesions are very similar to the Afghan hound myelopathy. However, the latter is a primary myelinolytic disorder. It is not clear from the description of this lesion in Kooiker dogs to what extent axons are spared. If, in fact, they are spared, then this lesion does resemble the Afghan hound myelopathy and should not be called a necrotizing myelopathy. If it is truly a funicular necrosis, then it is a unique lesion with no comparison to other recognized myelopathies.

References are on page 350.

MYELOPATHY IN MERINO SHEEP

A myelopathy affecting medium-quality-wool Merino sheep in Australia has been described by Harper.¹ Other sheep breeds on affected farms were spared. Diseased sheep comprised up to 2% of the flock and were identified by a progressively worsening paraparesis and ataxia. The pelvic limbs were basewide, the gait unsteady and swaying (truncal ataxia), and affected sheep would often collapse into a dog-sitting position. Thoracic limb and brain function were normal. Affected sheep were mostly between 5 months and 2 years of age, although some survived longer. Many died early in the course from misadventure or were killed.

Pathological findings were a Wallerian degeneration affecting white matter symmetrically in the dorsolateral tracts of the lateral funiculi and medial tracts of the ventral funiculi of the thoracic spinal cord. Chains of digestion chambers,

some containing macrophages, reflected axonal and myelin degeneration. Occasionally, degeneration was observed in the spinal roots. Degenerative changes in motor neurons in the ventral gray column and in brain stem populations were lacking, and serum copper levels were comparable to those of unaffected sheep.

Despite clinical and pathological similarities, it is thought that this myelopathy in Merino sheep is not due to copper deficiency (known colloquially as swayback or enzootic ataxia). On one farm, cases ceased when the ram was changed, while the sparing of cohabitating sheep of other breeds also suggests a possible genetic trait.

References are on page 350.

PROGRESSIVE DEGENERATIVE MYELOENCEPHALOPATHY OF BROWN SWISS CATTLE (WEAVER SYNDROME)

A familial, neurodegenerative disorder of Brown Swiss cattle has been described in the United States,¹ Canada,² and Europe. Breeding records indicate that certain families of Brown Swiss cattle have a predilection for the syndrome; inheritance is most likely recessive.³ Affected calves of both sexes show signs from 5 to 8 months of age.³ Their "weaving" gait is a truncal ataxia and is accompanied by pelvic limb spastic paresis and dysmetria and abnormalities of proprioception.⁴ The disorder is slowly progressive, resulting in recumbency by 1.5 to 3 years of age. Mild forelimb deficits precede recumbency.

At necropsy, there is atrophy of pelvic limb musculature. The changes in the CNS are microscopic, involving the spinal cord and caudal brain stem. Spinal cord lesions comprise axonal swelling and degeneration or lysis in the white matter. Secondary demyelination ensues, attended by a light microglial cell response. Liquefaction of distended axons (spheroids) imparts a spongy change to the tissue. Lesions are most severe in the thoracic segments of the spinal cord, particularly subpial areas of the ventral and lateral funiculi. Spheroids, in lower numbers, are found in the medulla oblongata. There is patchy loss of cerebellar Purkinje cells, with swellings of their proximal axonal segments (torpedoes) within the granule cell layer. Fine structural features of axon and myelin sheath degeneration in the spinal cord have been reported.⁵ Ultrastructural studies have also shown quantitative changes in cortical synapses of affected cattle;⁶ their significance must yet be determined.

This degenerative disorder of Brown Swiss cattle appears to be a primary axonopathy. The nature of the axonal changes, if not their topography, somewhat resembles those of neuroaxonal dystrophy.

References are on page 350.

PROGRESSIVE SPINAL MYELINOPATHY IN MURRAY GREY CATTLE

A progressive encephalomyelopathy is described in the Murray Grey breed of beef cattle in Australia.¹ The syndrome is inherited in an autosomal recessive pattern.² Calves, often affected at birth, are paraparetic and ataxic.

Histological examination reveals a diffuse myelopathy involving the dorsal spinocerebellar and ventromedian tracts. In advanced cases, peripheral (subpial) myelin in lateral and ventral funiculi shows a polycystic change. Chromatolytic neurons are found in the ventral gray column, nucleus thoracicus, red, lateral vestibular, and other brain stem nuclei. Wallerian degeneration is described as minimal, and therefore the progressive myelin loss is thought to be a primary demyelination. This seems unlikely, based on the tract distribution and the gray matter changes.

The neuropathology is reminiscent of several diseases. Copper deficiency is considered to be unlikely as adequate liver copper levels occur in the youngest affected calves. Vitamin E deficiency is worthy of consideration, but this might be a primary neuropathy involving the perikaryon and/or the axon.

References are on page 350.

CONGENITAL AXONOPATHY IN HOLSTEIN-FRIESIAN CALVES

A syndrome characterized by recumbency and weakness from birth has been described in Australian Holstein-Friesian calves.¹ Thirteen of 19 affected calves were descendants of a common bull. Many affected calves could achieve sternal recumbency but if wheelbarrowed would collapse. Stimulation could incite an opisthotonic posture, and recumbent calves often had forelimb extension. In some cases, head tremor and horizontal nystagmus were further neurological abnormalities. Several calves lacked a menace response, but a failure to elicit this protective reflex is common in the neonate.

At necropsy (1 to 7 days of age), a diffuse encephalomyelopathy was observed, most severe in the spinal cord and milder in the brain stem. All segments of the spinal cord were involved, lateral and ventral funiculi more than the dorsal columns. Tissue changes were of Wallerian degeneration, which was particularly pronounced at the periphery of the spinal cord. Axonal fragmentation and lysis were accompanied by myelin ballooning, disruption, and phagocytosis (Fig. 5-79); gliosis was mild to moderate. A few spheroids were observed. Lesions ascended from the cervical spinal cord into the brain stem to the level of the midbrain, and swollen axons abutted some brain stem nuclei; neuronal cell body loss was not evident. Several calves had mild lesions in peripheral nerves.

The cause of this encephalomyelopathy is not known, but an inherited basis seems likely. The degenerative process is thought first to affect the axon (or its cell body) with secondary loss of myelin.

A syndrome of congenital tremor was encountered in male Holstein-Friesian calves in the Netherlands.² Affected calves were all the progeny of one cow or her daughter. Postmortem investigations revealed a spongy degeneration of brain and spinal cord white matter with myelin and axonal loss. The investigators suggested that the disorder may result from a primary axonopathy.

References are on page 350.



Fig. 5-79. Holstein-Friesian calf axonopathy. Spinal cord degeneration. (H&E, $\times 350$.)

ENCEPHALOMYELOPATHY IN SIMMENTAL AND LIMOUSIN CALVES

A novel multifocal encephalomyelopathy has been recognized in 5- to 12-month-old **Simmental** and **Simmental-cross** calves in New Zealand, Australia, and the United States.¹⁻³ Affected calves develop a pelvic limb ataxia, waste away, and die within 6 months of developing clinical disease. Some cases show behavioral changes, including aggressiveness or dullness. Pathological changes are characterized by bilaterally symmetrical, multifocal grayish areas of degeneration in the internal capsule, caudate nucleus, putamen, brain stem, and spinal cord gray matter. Microscopically, an early spongy change of the neuropil proceeds to pannecrosis with liquefaction of neurons, their axons, and myelin sheaths. Necrotic tissue is invaded by proliferating capillaries and scavenger cells. Ultrastructural examinations have demonstrated abnormal mitochondria within skeletal muscles, but not within neurons or astrocytes, in an affected steer.⁴ Liver analysis in two affected Simmental calves revealed elevated aluminum and subnormal copper and manganese levels.³ The significance of this observation remains to be established.

These CNS lesions are similar to those observed in **Limousin**⁵ and **Limousin-cross** calves^{6,7} in Australia and England. These animals, from about 1 to 4 months of age, begin to lose weight and show forelimb hypermetria, aggressive behavior, and blindness. There is abnormal nystagmus of variable pattern and a bilateral, medial strabismus. These Limousin calves have multifocal, bilaterally symmetrical areas of grayish discoloration or cavitation in cerebral and cerebellar white matter, lateral geniculate nu-



Fig. 5-80. Limousin encephalopathy. Plaque of myelin degeneration in cerebellar peduncles.

cleus, substantia nigra, and optic chiasm. Histologically, there is early myelin spongiosis progressing to demyelination or to frank necrosis, the latter accompanied by astrogliosis, capillary proliferation, and macrophage activity. Lesions in the cerebellar peduncles may produce discrete demyelinated plaques (Fig. 5-80), and Schwann cell remyelination has been observed.⁷ There is loss of retinal ganglion cells and their fibers in the optic tracts. Mild to moderate Wallerian degeneration is found in the spinal cord.

Clinically and pathologically, these disorders of Simmental and Limousin calves have some shared features. The Simmental calves are not blind, and they lack the optic tract and cerebral white matter changes. A metabolic derangement is suspected but has yet to be identified. Similar multifocal degenerative brain lesions have been observed in a neurological disorder of **Angus** calves in Australia and the United States.

References are on page 350.

NEURONAL GLYCOPROTEINOSIS

Lafora body disease is a lethal epileptic human disorder, inherited as an autosomal recessive trait, with a presumed underlying metabolic basis. Clinical signs usually begin early in the second decade of life with generalized seizures, followed by the development of myoclonic jerks and ongoing mental deterioration. The disorder is progressive and fatal, usually within a decade of onset. Lafora bodies can be found in the CNS, skeletal and cardiac muscle, and liver. A form of progressive myoclonic epilepsy in children, unassociated with the formation of Lafora bodies, is also recognized.

By light microscopic, histochemical, and ultrastructural criteria, Lafora bodies are very similar to corpora amylacea and a few other inclusions found within the human CNS. To designate their composition of glucose polymers, some prefer the term **polyglucosan bodies**. Accordingly, a sporadic neurological disorder of late onset (and thus distinct from Lafora's disease), with inclusions in the CNS, has been designated adult polyglucosan body disease.¹

Lafora bodies have been observed in the CNS of **dogs** and a few other animals² under a variety of circumstances. They are observed in young adult dogs, especially **Beagles**, **Poodles**, and **Basset Hounds** with an antecedent history of seizures or other neurological disturbances such as depression or somnolence.³⁻⁵ In a 10-year-old **Corgi**, they were associated with myoclonic contractions of head and neck musculature.⁶ In many dogs, however, the postmortem observation of Lafora bodies in neurons is purely incidental.⁷ They are associated with aging,⁸ occurring particularly in dogs that are at least 8 years old.

Lafora bodies are 5- to 20- μ m basophilic, complex glycoprotein neuronal inclusions occurring in the perikaryon, dendrites, or axon (Fig. 5-81); they may be found anywhere in the neuraxis and in retinal ganglion cells. In dogs with neurological disease, they are particularly common in cerebellar Purkinje cells, especially their primary dendrites within the molecular layer, and in thalamic neurons. When encountered as an incidental finding, they may be found in these and other areas of the brain and in the spinal cord, most commonly in caudal lumbar, sacral, and caudal segments.⁹ Lafora bodies are approximately circular and may be homogeneous or have a dense nucleoid. Some are concentrically laminated, whereas others have a peripheral radiating pattern. They may occur in rows, and sometimes a couple are found fused together. They are PAS-positive and also stain with alcian blue and methenamine silver. Lectin studies show binding by concanavalin A,¹⁰ indicating the presence of mannose as well as glucose within the complex glycoprotein. Ultrastructurally, they are found to have fibrillary and electron-dense, sometimes granular components in varying proportions.^{4,8,11} They are not membrane-bound and appear to be associated with, and perhaps derived from, rough endoplasmic reticulum and Golgi.

References are on page 350.

MISCELLANEOUS BOVINE ENCEPHALOPATHIES

In the course of the bovine spongiform encephalopathy (BSE) epidemic in the United Kingdom many cattle have been killed as suspected BSE cases. Some cows, negative for BSE, have revealed novel encephalopathies including brain stem neuronal chromatolysis and hippocampal sclerosis and substantia nigra vacuolation.¹⁻³

References are on page 350.

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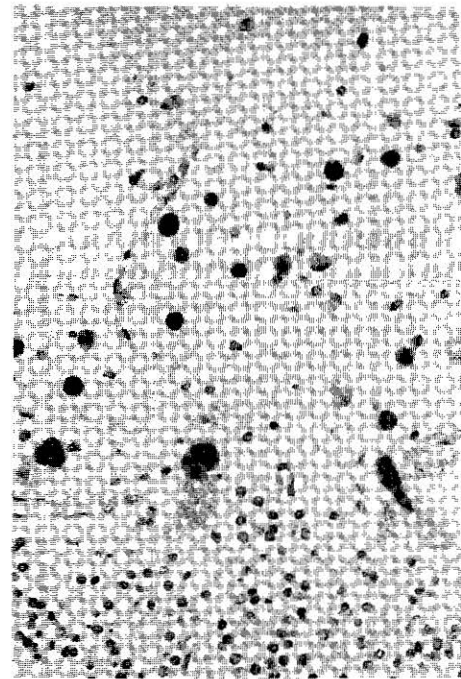


Fig. 5-81. Neuronal glycoproteinosis. Lafora bodies, cerebellar cortex, dog. (PAS, $\times 350$.)

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Chapter 6 TUMORS OF THE CENTRAL NERVOUS SYSTEM

INTRODUCTION

A considerable literature describes the occurrence of spontaneous tumors of the CNS in animals. Of the domestic species, most examples are seen in the dog,^{1,2} and the spectrum that has been described is quite broad. These tumors are less common in the cat, and meningiomas and lymphomas account for the majority. Within the other domestic species, neoplasms of the brain and spinal cord are distinctly uncommon. These tumors are also described in the laboratory animal species, especially mice and rats maintained for lifetime studies. In these species it has been possible to associate particular tumors with certain animal strains (e.g., astrocytomas in the inbred VM strain of mice).

A systematic study of CNS tumors of animals has been undertaken by few veterinary neurologists or neuropathologists. Information on the incidence of CNS tumors is available only for the dog and is perhaps 1% to 3% of all canine necropsies. Clinicopathological correlations with CNS tumors of dogs are described by Palmer and colleagues,^{3,4} Fankhauser and Vandeveld,⁵ de Lahunta,⁶ Braund,⁷ and Nafe⁸ for dogs and cats. These neoplasms typically cause progressive neurological signs in aged animals. Seizures and behavioral changes are common. Many produce localizing signs that are determined by neurological examination and allow a reasonably precise anatomical diagnosis to be reached. However, secondary changes, such as obstructive hydrocephalus (Fig. 6-1), cerebral edema,⁹ herniations,¹⁰ and tumor spread within the brain may produce more widespread deficits. Ophthalmoscopic examination occasionally reveals papilledema.⁴ Reports employing contemporary techniques such as computerized tomography for imaging brain tumors in animals are now appearing in the veterinary literature.¹¹⁻¹³ Such studies will be important in the evaluation of therapeutic protocols,¹⁴ particularly if such cases are used for comparative medical purposes. Nuclear magnetic resonance offers an even higher level of tumor definition, but the relatively higher cost associated with this instrument will probably limit its clinical use for animals.

At our own institution, we have been highly satisfied with the older technique of radioisotope scanning using technetium-99.^{15,16} Electroencephalographic patterns do not appear to be specific for brain tumor type or location.¹⁷

Analysis of CSF is commonly performed in the clinical study of patients with neurological disease. Variable changes in CSF pressure, white cell count, and total protein content are found in dogs with primary brain tumors.¹⁸ In dogs with meningiomas, the presence of neutrophilic influx into these tumors is reflected by a predominance of this cell type in the CSF. Only rarely have neoplastic cells been identified in the CSF in animals with brain tumors.^{19,20}

Morphological studies of series of spontaneous neoplasms of the CNS in animals have been reported by Dahme and Schiefer,²¹ McGrath,²² Innes and Saunders,²³ Luginbühl and colleagues,²⁴ Hayes and Schiefer,²⁵ Fankhauser and others,²⁶ and Zaki.²⁷ A most comprehensive treatise is provided by Fankhauser and Luginbühl.²⁸ Most cases have been in dogs and cats; reports of any number in other domestic species are few.²⁹ Contemporary reports of human CNS tumors invariably include immunocytochemical studies, and recently lectin binding patterns in human gliomas have been examined.³⁰ One comprehensive immunohistochemical study of canine neuroectodermal tumors has been published by Vandeveld and associates.³¹ The authors conclude that relatively more canine brain tumors are undifferentiated (and difficult to classify) than is the case for human gliomas. Fankhauser and associates²⁶ were unable to classify 15% to 20% of the small animal gliomas they studied and even fewer of the gliomas of farm animals.

Although our primary concern in this volume is with spontaneous disease, several model systems of experimental CNS neoplasia have been exploited. Such include the administration of nitrosourea compounds to pregnant rats,³² which induces gliomas in their progeny, avian sarcoma virus-induced gliomas in dogs,³³ and a canine gliosarcoma cell line, derived from an avian sarcoma virus-inoculated dog; this neoplasm may be transplanted intracerebrally.³⁴ It is also of interest that the establishment, from spontaneous

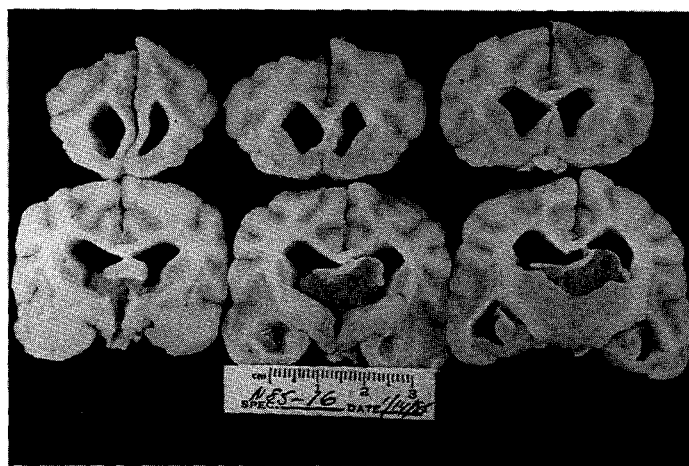


Fig. 6-1. Hydrocephalus resulting from an intraventricular mass (choroid plexus papilloma of the third ventricle), dog.

tumors, of two canine astrocytoma cell lines and their transmission to nude mice have been reported.³⁵

The consistent occurrence of certain neuroectodermal tumors in particular areas of the brain, a phenomenon well recognized in humans, implies that their genesis is not a random process. Discrete populations of cells within the neuraxis, with active and persistent mitotic activity, would be at the greatest risk, should the organ be exposed to carcinogens. The germinal subependymal plate is one such area and may explain the impression that some gliomas in the dog arise in this zone.³⁶ Transformation of cells in the subependymal zone could occur early in life, during the time of greatest mitotic activity, perhaps resulting in tumor formation after a long latent period. Then again, persistent low-level mitotic activity in this tissue would facilitate neoplastic change at middle age and later in life. Rubinstein and associates³⁷ have listed several cellular populations of continuing neurocytogenesis which may be at risk. Such include the external germinal cell layer of the cerebellum, a possible source of the human medulloblastoma. In the rat, a subpial target cell population for *N*-ethyl-*N*-nitrosourea-induced gliomas has been identified in the spinal cord.³⁸

Many broad aspects of the biology of CNS neoplasia are areas of active investigation in humans; comparable studies in animals with spontaneous CNS tumors are largely unknown. It is well recognized that human patients with primary CNS malignancies, particularly those of high grade, have impairment of their immune system.³⁹ For example, intrinsic defects of T-cell function,^{40,41} depleted levels of circulating T-helper/inducer cells,⁴² and T-cell suppressor factors (such as transforming growth factor- β)⁴³ produced by glioblastoma cells⁴⁴ have been described. Furthermore, glioma cell lines can produce a protective mucopolysaccharide coating that, in vitro, impairs the generation of specific cytotoxic lymphocytes.⁴⁵ The expression of adhesion molecules by glial tumors may be important for local invasiveness and for the interactions between tumor and

immunocompetent cells.⁴⁶ Other areas of ongoing investigation include the expression of normal and neoantigen gliomas of man and in chemically induced gliomas of laboratory animals,^{47,48} one goal being the capacity for select delivery of chemotherapeutics to inoperable tumors.⁴⁹ Finally, the heightened expression of certain oncogenes; the role of growth factors in primary human neural tumors are of current interest,⁵⁰⁻⁵³ and the use of molecular biological techniques in tumor evaluation may become routine.

References are on page 394.

MALFORMATIONS, HAMARTOMAS, CYSTS, AND BORDERLINE TUMORS

This small section covers a group of miscellaneous conditions marked by cell proliferation or cyst formation. The appropriate classification is often problematic, and the terminology employed is at times confusing (e.g., angioma as one form of vascular malformation). Several of the disorders involve the vasculature, and so, for convenience we have presented all CNS vascular malformations here rather than in Chapter 2.

Hamartomas are masses formed by disorderly overgrowth of tissue elements normally present at that site. They differ from neoplasms in that they are not autonomous and their growth is finite. In some cases, for example vascular hamartomas, separation from true neoplasms is difficult and at times arbitrary. In humans **hypothalamic hamartomas** are well recognized, arising from the tuber cinereum or mammillary bodies. They contain abnormal, vacuolated neurons admixed with glial cells. They are very rarely reported in the dog.^{1,2}

Malformative vascular lesions, of considerable importance in human neuropathology, are viewed as hamartomas of blood vessels.³ These include the arteriovenous malformations, capillary and venous ectasias (telangiectases), cavernous angiomas, and congenital (saccular) aneurysms. In humans, arteriovenous malformations are the most common

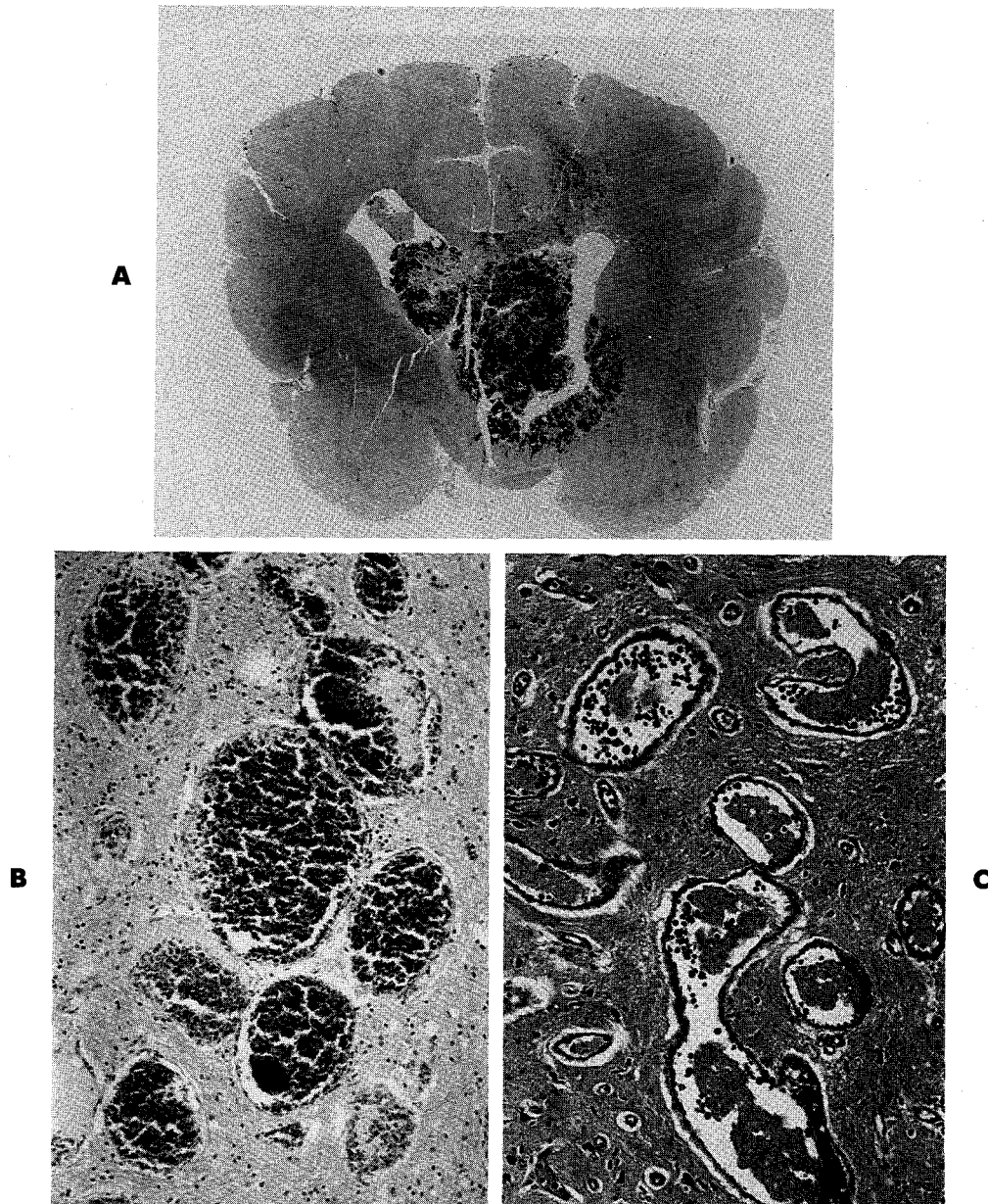


Fig. 6-2. A, Midline vascular hamartoma, dog. (H&E, $\times 2$.) B, Detail of cavernous blood vessels. (H&E, $\times 140$.) C, Venous hamartoma, cerebral cortex, horse. (Masson's trichrome, $\times 140$.)

mon. These malformations of abnormally proliferated immature blood vessels result in the formation of multiple direct arteriovenous communications without an intervening capillary bed.⁴ These are congenital disorders that may not produce clinical signs until patients are adults. Clinical signs result from the space-occupying nature of the lesion and from episodes of ischemia or hemorrhage. Vascular malformations are uncommon in the CNS of domestic animals, and relatively few comparable cases have been documented in veterinary neuropathology.⁵ Fankhauser, Luginbühl, and McGrath⁶ described the vascular malformations of the CNS that they have encountered in animals; most were seen in

the dog. Interestingly, these dogs did not present early in life but were mature to aged (6 to 17 years). These structures consisted of accumulations of arteries, veins, and capillaries of unusual size and structure. We have observed a large vascular mass involving the septal area and thalamus in a 13-year-old Poodle dog that was depressed and circled; a vascular hamartoma (cavernous angioma?) was diagnosed (Fig. 6-2, A and B). Cordy⁵ has described a spinal leptomeningeal arteriovenous malformation that contained distended, tortuous, and thick-walled arteries and veins in a young dog. Vascular malformations have been reported involving the spinal cord of a calf and a foal.^{7,8}

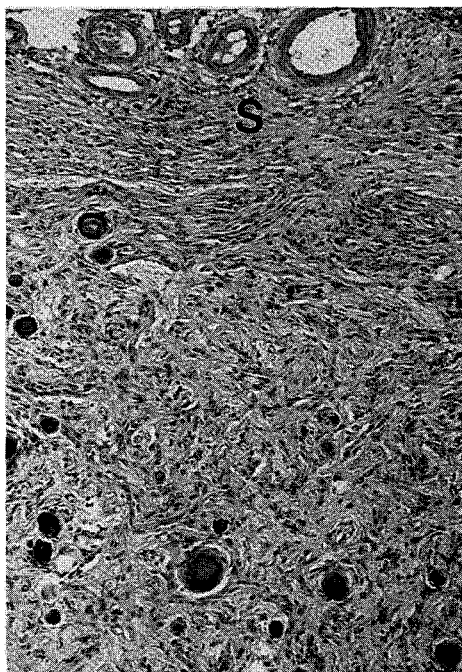


Fig. 6-3. Meningoangiomatosis, human. Cellular proliferation, associated with supernumerary blood vessels, fills the subarachnoid space (s) and infiltrates the underlying cerebral cortex. Notice psammoma bodies. (H&E, $\times 140$.)

Ribas and co-workers have described **meningoangiomatosis** in a dog and compared it to one human case.⁹ This is a rare proliferative disorder (malformation? hamartoma?) of leptomeningeal blood vessels and spindled elements thought to be meningothelial cells (Fig. 6-3). The proliferative mass forms a grossly visible plaque that invades the adjacent neural parenchyma. Characteristically, the spindle-shaped cells extend from the subarachnoid space into the brain along perivascular spaces. They may be fibroblastic rather than meningothelial.¹⁰ Stebbins and McGrath¹¹ have also reported a similar case in a dog. A case report of a horse with seizures described a **meningocerebral hemangiomas**.¹² The cerebral leptomeninges of one hemisphere were thickened because of the presence of redundant arteries and veins (Fig. 6-4). The underlying cortex was dysplastic and lacked normal neuronal lamination. A further curious feature was an onion bulb neuropathy that affected the trigeminal nerve and ganglion. Analogies with the human phakomatoses, particularly Sturge-Weber disease, were made.

In **borderline tumors**, the distinction between hamartoma, malformation, and neoplasia is unclear. For example, McGrath¹ has studied a series of "angiomas," which he believes are malformations rather than true tumors. Vascular masses designated as **hemangiomas** have been reported in the spinal cord of the dog⁵ and horse¹³ and in the brain of the dog.¹ **Lipomas**, so-called, are observed as extramedullary masses in mice,¹⁴ pigs,^{15,16} and sporadically other spe-



Fig. 6-4. Meningeal hemangiomas, horse. Cerebrum. (Masson's trichrome, $\times 140$.)

cies (Fig. 6-5).¹⁷ They are usually discrete masses of mature adipose tissue, sometimes admixed with cartilage or other mesenchymal elements. They are often located in the choroid plexuses or in the midline leptomeninges. They can be considered malformative or hamartomatous. In the human vertebrae, they may be found in association with spina bifida and meningocele.

A variety of **cystic lesions** are recognized within the CNS of humans, including **ependymal cysts**, **endodermal cysts**, and **colloid cysts** of the third ventricle.¹⁸ Fewer have been described in animals. **Epidermoid cysts** within the neuraxis are akin to those encountered by dermatopathologists. A few have been reported in the **dog**;¹⁹⁻²¹ as in humans, they commonly occur in the cerebellomedullary area. Some become large enough to produce signs of neurological dysfunction; others are incidental findings at autopsy.²² Their common detection in young dogs suggests that they are congenital, although they have been seen in mature and aged dogs and so apparently can remain small for extended periods. Epidermoid cysts may form when the neural tube is closing and adjacent skin-determining ectoderm and mesoderm remain attached to the neural tube and become enclosed in the meninges as they form. Grossly, they present as smooth, pearly white, cystic structures up to 3 cm in diameter within the fourth ventricle, compressing the cerebellum and medulla. Microscopically, the cyst wall consists of a stratified squamous epithelium, supported by connective tissue stroma. Within the cyst are

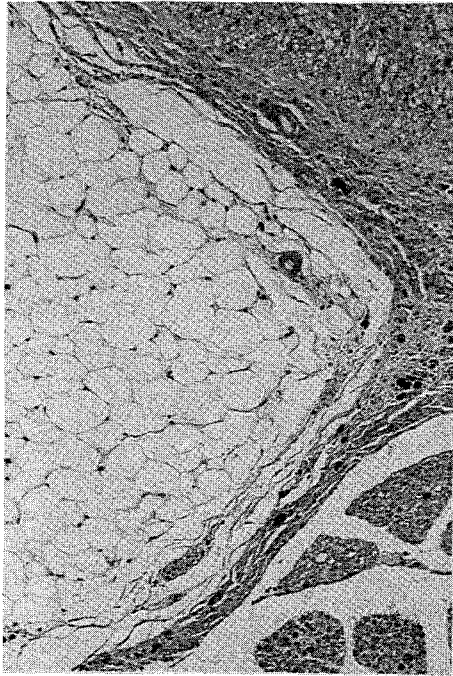


Fig. 6-5. "Lipoma." Spinal cord, cat. (H&E, $\times 140$.)

found keratin squames and a few inflammatory cells.

Reports in other domestic species are sporadic (Fig. 6-6).²³ Spinal epidermoid cysts have been noted in the lumbosacral leptomeninges of mice.²⁴ Although some produced compression of the cord and nerve roots, the animals were clinically normal. They have also been observed incidentally in the spinal meninges of rats.²⁵ In **dermoid cysts**, the cyst wall is complex and contains adnexa (sweat glands, hair follicles, and sebaceous glands).^{1,26,28} Precisely how epidermoid and dermoid cysts should be classified is uncertain. Whereas some view them as purely malformative, the opposing case is that they are expressions of a teratoma in which a single somatic cell layer predominates.²⁸

Spinal **arachnoid cysts** have been observed in a few dogs, occurring as dorsal, intradural-extramedullary CSF-filled structures.^{29,30} They may cause spinal cord compression, and at times their detection may be incidental. The pathogenesis of these cysts is unknown.

References are on page 395.

MENINGEAL TUMORS

Meningiomas are important tumors of the human CNS. Systematic study of these neoplasms has shown a remarkable histopathological diversity¹ with both mesenchymal and epithelial patterns. This spectrum may reflect the fact that both mesoderm and neural crest contribute to the formation of the meninges.² The range of patterns recognized in human meningioma includes fibromatous, lipomatous, myxomatous, chondro-osseous, angiomatous,

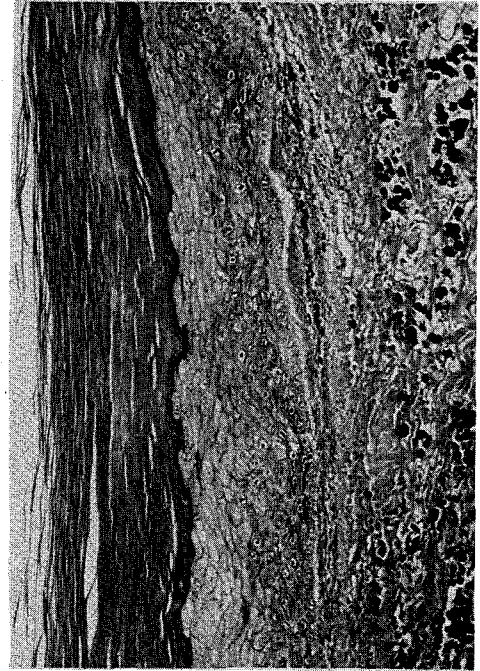


Fig. 6-6. Epidermoid cyst, cerebrum, horse. Black granules are hemosiderin deposits within connective tissue. (H&E, $\times 140$.)

and hemangiopericytic forms. Other variants are epithelial, including papillary, pseudoglandular, and secretory forms.^{3,4} Furthermore, meningiomas may mimic other tumors, including astrocytomas, oligodendrogliomas, and metastatic carcinomas.¹ This may lead to misdiagnosis and even initiate the search for a nonexistent, extraneural primary tumor.

The ultrastructural features of human meningiomas have been studied,⁵ and more recently developed immunocytochemical techniques have been applied in their investigation. Vimentin is the predominant intermediate filament type that they express;^{6,7} epithelial variants contain keratin while many, regardless of pattern, are positive for the epithelial membrane antigen.^{4,8}

In the animal species, meningiomas are encountered most frequently in dogs, cats, and rats. Reports of this tumor in the other species are sparse; see Luginbühl and others⁹ and Innes and Saunders¹⁰ for references.

Canine meningiomas are quite common, particularly in mature and aged dogs, and McGrath¹¹ has studied more than 100. Meningiomas in humans are more common in the female, and McGrath's series shows this trend also, with 64 in female and 39 in male dogs. As in humans, meningiomas in the dog and cat have receptors for estrogen, progesterone, and androgen,¹² which may influence the growth and behavior of these tumors.

Study of the distribution of meningiomas within the neuraxis has become quite a science in humans. These tumors are believed to be derived from the arachnoid cap cells and arachnoid granulations, particularly where arachnoid cells

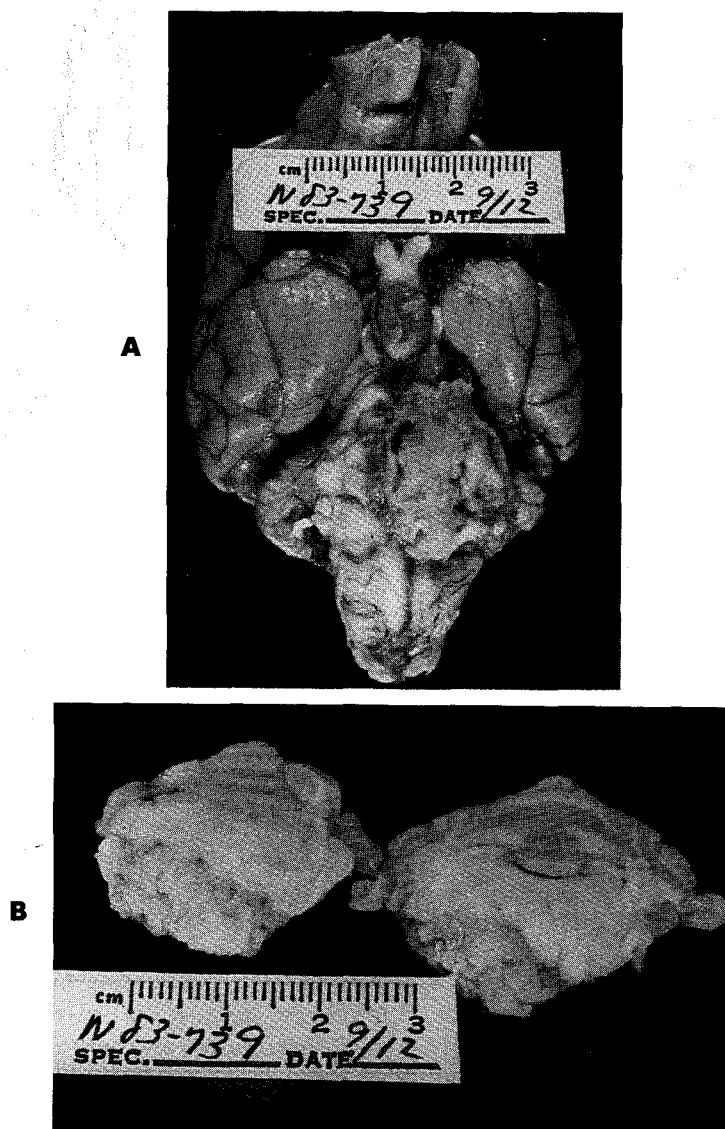


Fig. 6-7. A and B, Pontomedullary meningioma, dog.

project into the dural venous sinuses. Hence meningiomas are regularly attached to the dura and occur at particular sites with some regularity. In the dog, our knowledge is very limited; they are much more common in the brain than the spinal cord.¹³ Within the cranium they occur over the convexities, in the midline attached to the falx cerebri, below the brain stem, attached to the tentorium cerebelli, or at an intraventricular location associated with a choroid plexus (Figs. 6-7 and 6-8). Rarely, they are retrobulbar. Clinical signs they incite depend on their location, speed of growth, and secondary effects (such as brain swelling and herniations); many are associated with a progressive course of neurological signs developing over some weeks to months. Circling, propulsive gait, visual loss, seizures, and cranial nerve deficits commonly occur.¹⁴ Spinal meningiomas result in deficits reflecting spinal cord and/or root compression.^{15,16}

Grossly, meningiomas are discrete, firm to rubbery, somewhat lobular, gray to pink, extramedullary masses. Hemorrhage imparts a reddish color, which may be more evident upon sectioning. Hyperostosis, a proliferative bony response to pressure that is a hallmark of human meningiomas, is described in animals.⁹ Where they impinge on the brain or spinal cord, most show compression rather than infiltration. Their attachment to the dura or leptomeninges may be broad (sessile), narrow (pedunculated), or total (meningioma en plaque). Ventricular meningiomas are presumed to arise from the tela choroidea, the pia mater of the choroid plexus. Histological patterns that parallel the most important variants seen in humans are recognized in the dog (Figs. 6-9 and 6-10).^{13,17}

1. **Meningothelial** or **syncytial** types contain nests and lobules of neoplastic meningothelial cells delineated by fine, collagenous fibers. Cells have ovoid vesicular

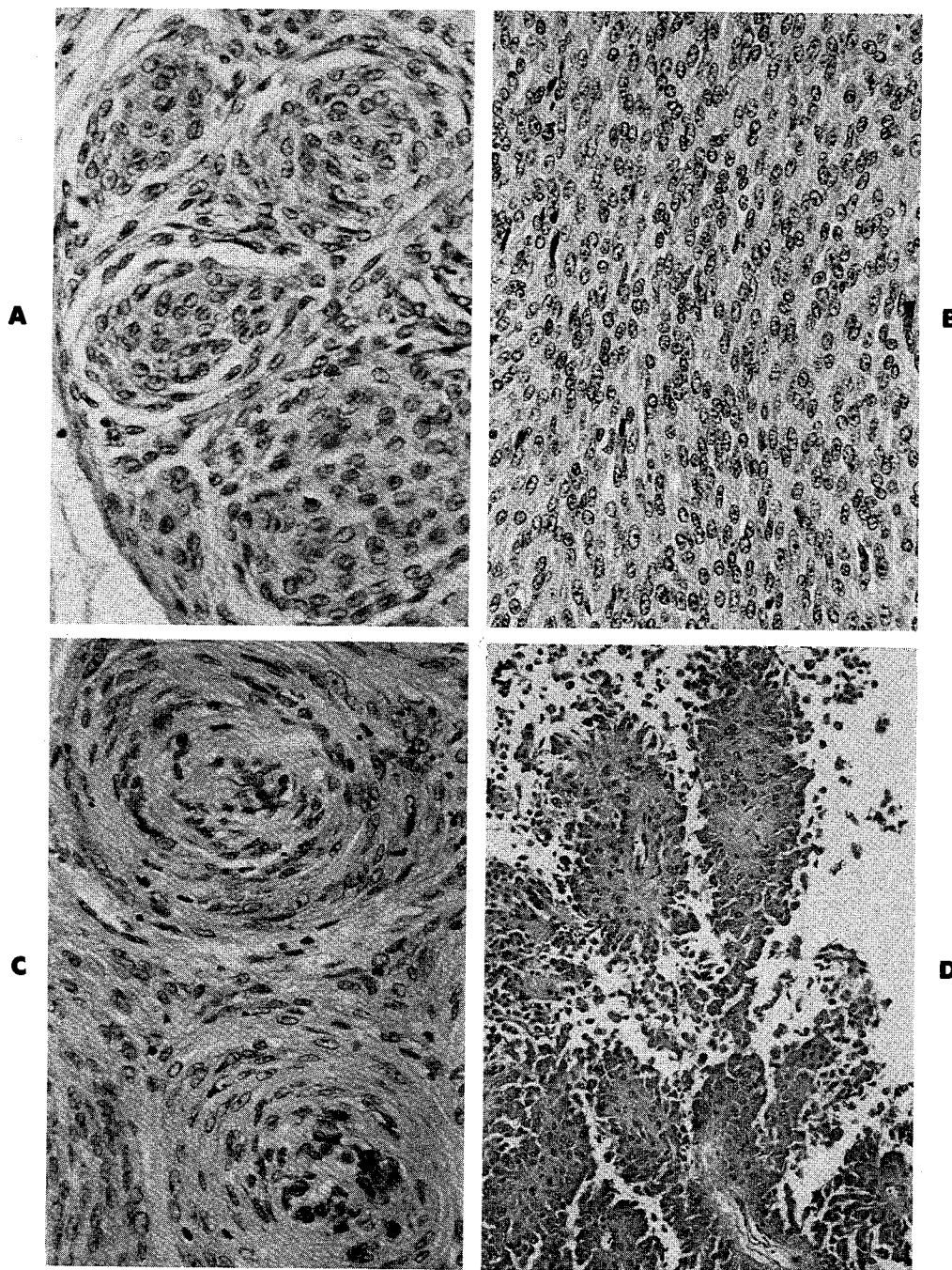


Fig. 6-9. Patterns in canine meningioma. **A**, Syncytial. (H&E, $\times 450$.) **B**, Fibroblastic. (H&E, $\times 350$.) **C**, Transitional. (H&E, $\times 350$.) **D**, Papillary. (H&E, $\times 140$.)

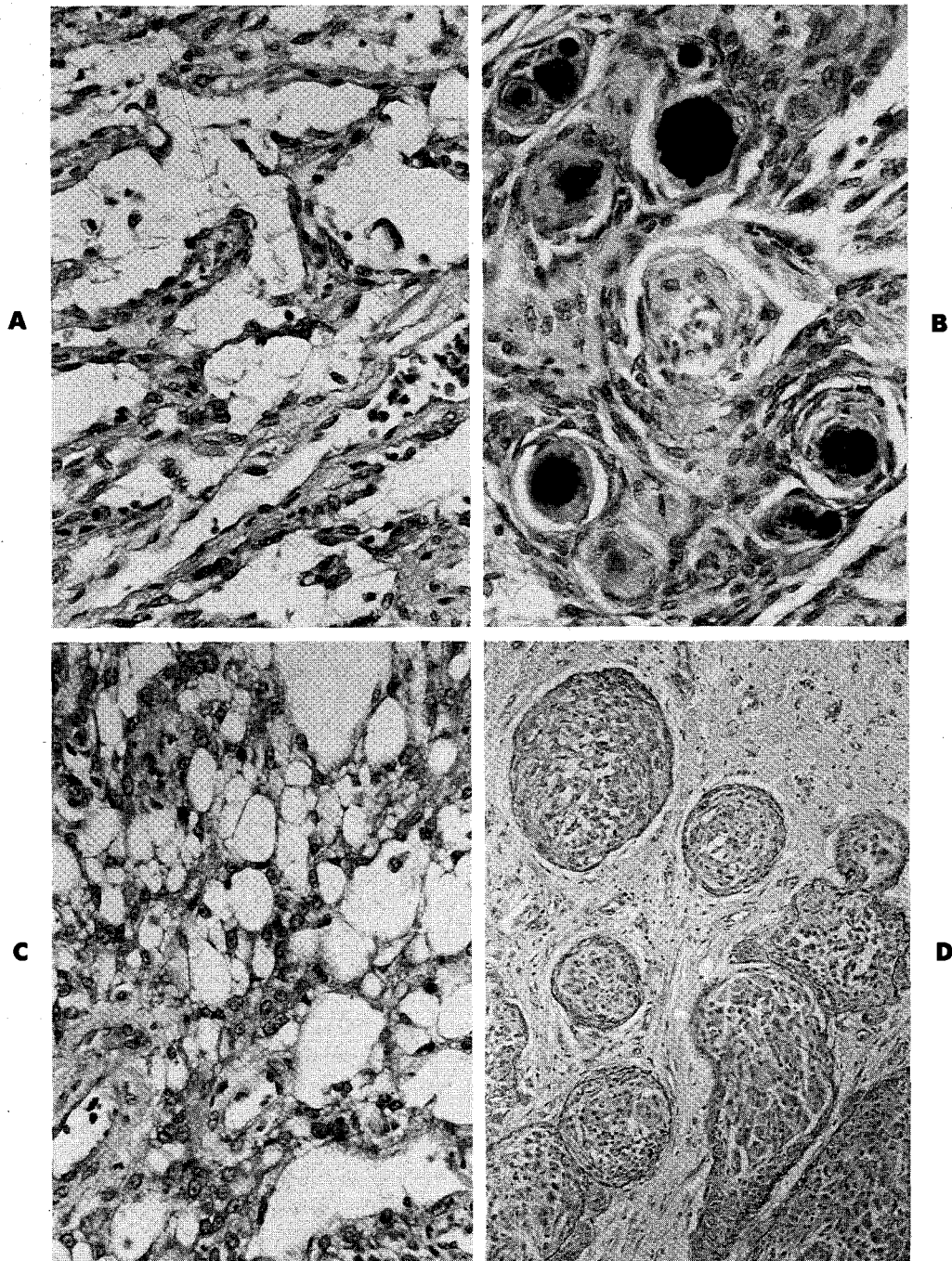


Fig. 6-10. Patterns in canine meningioma. **A**, "Angioblastic." These structures, which simulate vascular channels, were negative for Factor VIII-related antigen in this case. (H&E, $\times 350$.) **B**, Psammomatous. (H&E, $\times 350$.) **C**, Microcystic. (H&E, $\times 350$.) **D**, Aggressive meningioma infiltrating medulla. (Acid orcein giemsa, $\times 140$.)

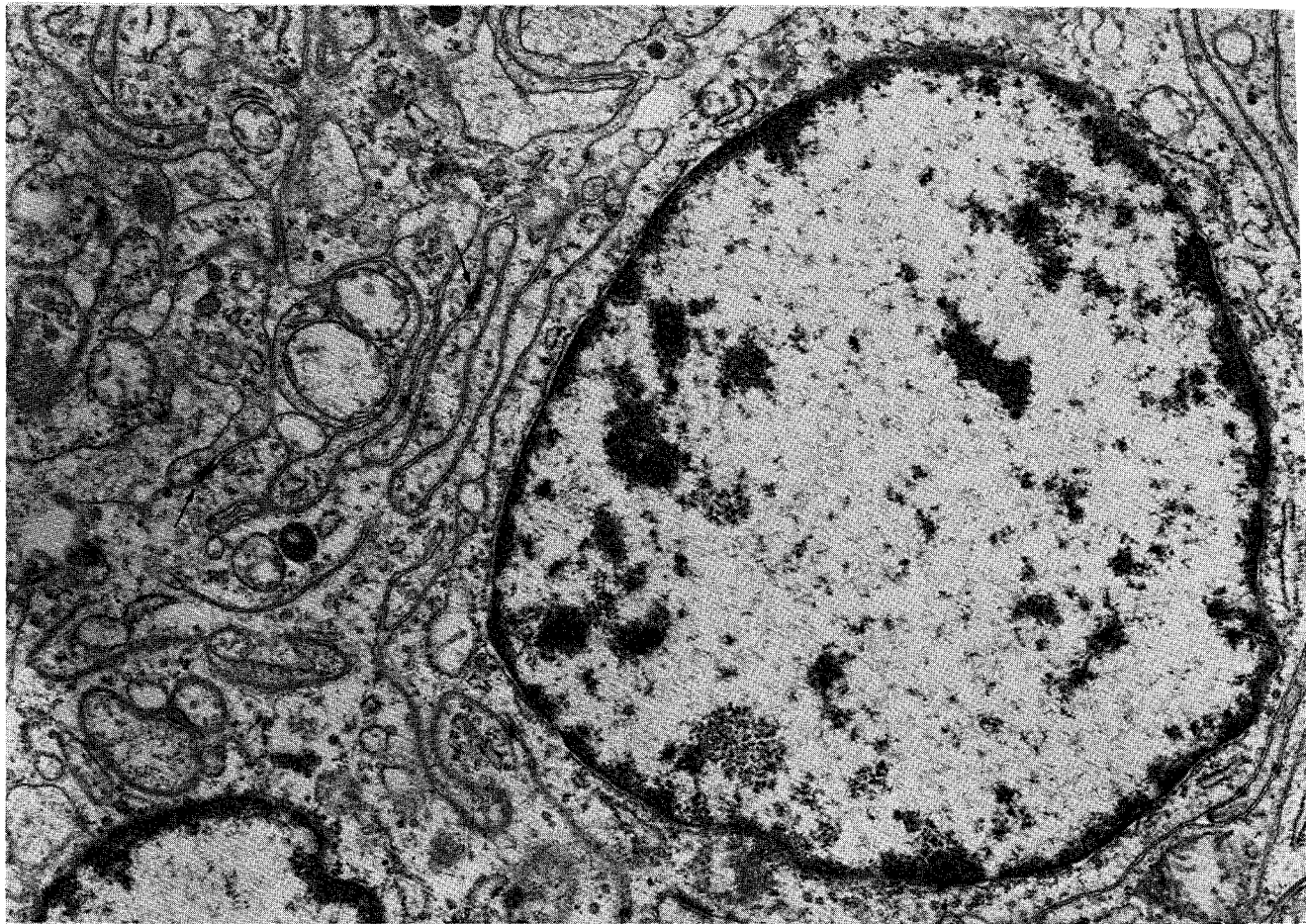


Fig. 6-11. Ultrastructure of canine meningioma. There is a large euchromatic nucleus. The cytoplasm forms extensively folded processes with scattered desmosomal junctions (arrows). ($\times 14,000$.)

nuclei, often a prominent nucleolus, and abundant cytoplasm with indistinct margins.

2. **Fibroblastic** forms are as fibromas elsewhere, with interlacing bundles of slender fibroblastic cells.
3. In **transitional** forms (admixture of syncytial and fibroblastic meningiomas), a prominent feature is concentric whorls of cells.
4. **Angioblastic** meningioma encompasses two entities in man. In one, thin-walled capillary and sinusoidal vascular spaces separate sheets of ovoid to spindle-shaped neoplastic cells. The tumor is rich in reticulin. This is the meningeal hemangiopericytoma, and whether this is truly a meningioma or rather is related to the soft tissue hemangiopericytomas is controversial; the latter view appears to be prevailing.^{18,19} In contrast to ordinary meningiomas, they have a propensity for local recurrence and even extraneural metastasis.²⁰ The other entity is the meningeal hemangioblastoma, which consists of small capillary vessels and interstitial or stromal cells, which are vacuolated

and may be swollen with lipid. Although a few canine tumors have been designated angioblastic meningiomas,¹⁷ microscopically they appear to be different than either of the human types.

5. In **psammomatous** patterns, small whorls of neoplastic cells or even blood vessels become hyalinized (degenerate) and encrusted with calcium salts, forming psammoma bodies.
6. In **microcystic** forms, individual lobules of a meningioma undergo a spongy, vacuolar change, producing a cribriform appearance.

Further variants can be listed, and mixtures of the various patterns are common; for example, a few psammoma bodies or focal microcystic change may be found in a transitional meningioma. We have observed papillary meningiomas in the dog, and one was reported in 1992.²¹ In general, the histological pattern seems to be of little prognostic importance in human meningiomas, apart from the papillary variant, which is aggressive, and the hemangiopericytoma, which frequently recurs. In any human meningioma, areas

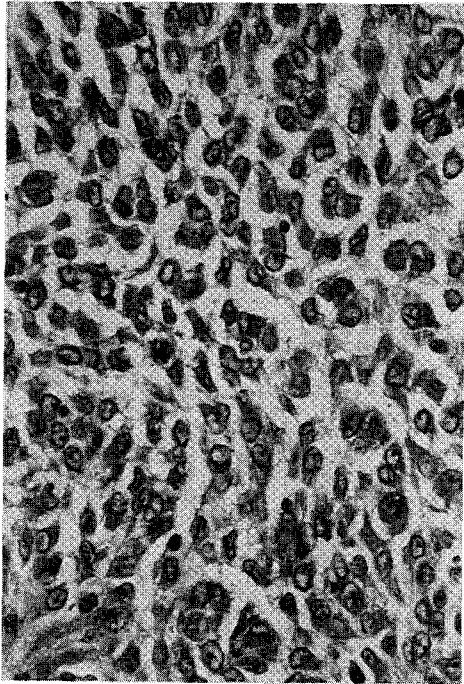


Fig. 6-12. Vimentin immunocytochemistry in a canine meningioma. ($\times 560$.)

of tumor necrosis, the presence of mitotic figures and brain invasion are taken as indicators of a poor prognosis, whereas evaluation of the nucleolar organizer regions within meningiomas may also have prognostic value.²² In contrast to humans, many canine meningiomas have areas of focal necrosis, with pools of neutrophils, and some show invasion along Virchow-Robin spaces. Impression smears, prepared at craniotomy, can be helpful in identifying an intracranial tumor as a meningioma.²³

Ultrastructural studies of human meningiomas show cells with extensive interdigitations of their cytoplasmic processes. Intercellular desmosomal junctions are common, and the processes contain accumulations of intermediate filaments.^{5,6} Such features are also characteristic of canine meningiomas (Fig. 6-11).¹¹ Canine meningiomas commonly express vimentin intermediate filaments (Fig. 6-12).

In humans, extraneural meningiomas are occasionally reported, including those within paranasal sinuses. Paranasal meningiomas have been reported in dogs.²⁴ Metastasis of intracranial meningioma to the lungs has been reported in three dogs.²⁵

Primary **sarcomas** of the meninges in dogs, such as fibrosarcoma, are rare and have no special features. A disseminated pleomorphic, lymphoreticular sarcoma of the leptomeninges is seen in the dog (Fig. 6-13) and has been designated **meningeal sarcomatosis**.⁹ Involvement of the full length of the spinal cord may occur; tumor bulk is often



Fig. 6-13. Pleomorphic meningeal sarcoma, dog. Cells express muscle actin, particularly at the cell membranes. Note binucleated and multinucleated cells. (Immunocytochemistry, $\times 350$.)

maximal at the lumbosacral end. These tumors extend from the subarachnoid space into the subpial parenchyma of the spinal cord (usually less so in the brain) and through the dura into epidural fat and spinal nerves. Cell types are lymphoid, plasmacytoid, mature plasma cells, immunoblastic cells with open-faced vesicular nuclei, and scattered multinucleated giant cells. A few cases have been reported recently²⁶⁻²⁸ (sometimes as meningeal lymphoma), and we have had experience with two.

Meningiomas are the most common primary CNS tumor of **cats**,²⁹ and at some institutions, cats with meningiomas are treated surgically.³⁰ These tumors occur at middle age or beyond except for the curious occurrence of meningiomas in young cats with mucopolysaccharidosis type 1.³¹

There is in cats a slight predominance in males (3:2),^{31,32} and they further differ from the dog in their tendency to be multiple. Meningiomas are quite common incidental findings at autopsy in the aged feline.^{32,33} Their topography is similar to that of humans and dogs, most being located rostral to the tentorium. A supraventricular location is relatively more common, particularly involving the tela choroidea of the third ventricle (Fig. 6-14). Microscopically, they are much more stereotyped than in the dog; most are meningotheliomatous or psammomatous, and many have cholesterol deposits.

Meningiomas are rare in other domestic species; they are reported in the horse, cow,³⁴ and sheep.

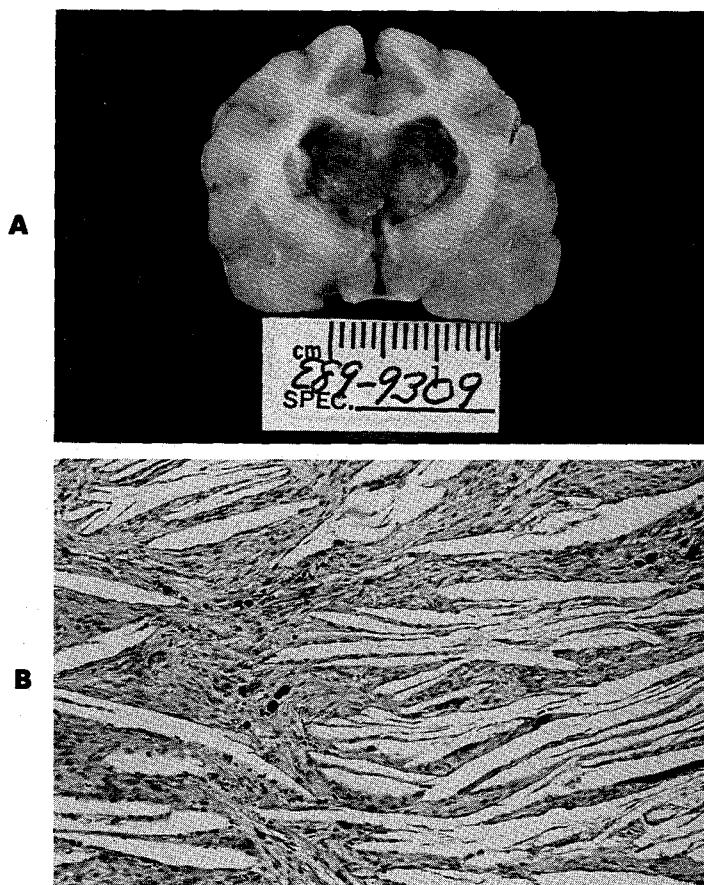


Fig. 6-14. Meningioma, cat. **A**, Meningioma dorsal to the third ventricle elevating the fornix. **B**, Prominent cholesterol deposition and hemosiderin granules. (H&E, $\times 140$.)

Meningiomas are seen in **mice**³⁵ and **rats**³⁶ maintained for lifetime studies and doubtless occur in geriatric pet rodents. Clinicopathological correlates are difficult to establish for meningiomas and for primary intramedullary tumors (gliomas, ependymoma, etc.) in rodents. Clinical signs in mice with brain tumors are nonspecific,³⁵ and in one series, only 12% showed clinical signs that pointed to a CNS neoplasm. Although these rodent populations are generally maintained for toxicological studies, the fairly equal distribution of CNS tumors in both treated animals and control groups suggests that they are spontaneous.

Of numerical importance are **granular cell tumors** of the meninges that occur in several strains of rats, including Sprague-Dawley,³⁷ Osborne Mendel, and Fischer 344.³⁸ They vary from microscopic to 1 cm in diameter and occur over the cerebral convexity, in the longitudinal cerebral fissure, over the cerebellar hemisphere, or beneath the brain stem. Males are more frequently affected than females. Microscopically these consist of a solid lobulated mass that compresses the adjacent neural tissue. Lobules contain sheets of tightly packed polygonal cells with vesicular nuclei

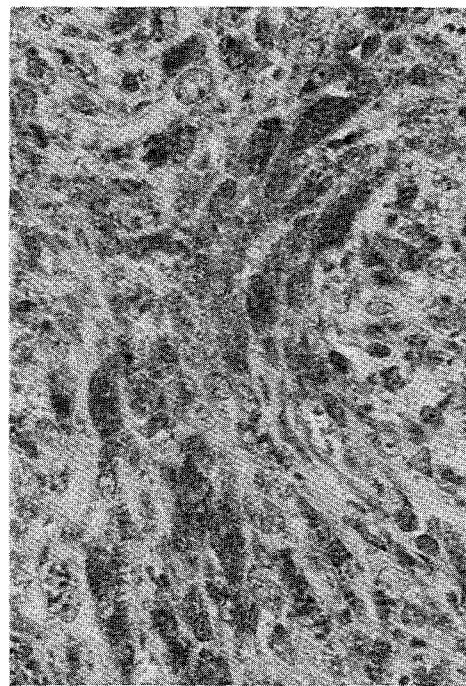


Fig. 6-15. Granular cell meningioma, rat. (PAS, $\times 560$.)

and eosinophilic granular cytoplasm that is PAS-positive (Fig. 6-15). A minor population of cells has dense cytoplasm with few granules and dark, pyknotic nuclei. Ultrastructural findings are consistent with granular cell tumors elsewhere, namely, membrane-bound primary and secondary lysosomal bodies,^{37,39} which fill the cytosol. These have been considered to arise from Schwann cells. However, the case has been made that mixed forms of meningotheial meningioma and granular cell tumor of the meninges occur in the rat.³⁸ Furthermore, the granular cells are S-100-negative, weakly vimentin-positive, and lack a basal lamina—further support for a meningotheial rather than a Schwann cell origin.³⁹ Mitumori and co-workers³⁸ also describe classical meningiomas (fibroblastic and meningotheial) and meningeal sarcomas for the rat.

References are on page 396.

ASTROGLIAL TUMORS

Tumors of astrocytic origin are common in humans¹ and some of the animal species. From studies of human astrocytomas over many decades, systems of classification have evolved, as has the recognition of certain clinicopathological patterns for astrocytomas at specific areas of the neuraxis. Thus infratentorial astrocytomas are predominantly seen in childhood; commonly involve the cerebellum, at which site they tend to become cystic; and carry a relatively favorable prognosis. In contrast, cerebral astrocytomas are most common in the fourth and fifth decade, often undergo malignant change, and so have a much less favorable outcome. Such

a spectrum is not recognized for gliomas in animals, which tend to present in aged patients and usually result in the animal's demise at that time. Thus few astrocytomas of dogs, for example, have been studied sequentially to establish whether progressive anaplastic change occurs within the tumor, as is recognized in some of the human counterparts.

Astrocytomas come in all shapes and sizes. Most are single masses, but dissemination within the neuraxis is observed in a proportion of the more malignant variants. Spread outside the neuraxis is recognized in humans, sometimes after surgical intervention, but seems not to occur spontaneously in animal varieties.² Their gross appearance reflects their cellular composition, degree of differentiation, and presence or absence of hemorrhage or necrosis. Many present as diffusely infiltrative growths that are difficult to define with respect to their margins, where they admix with neurons or myelinated axons. The affected area of the brain may be visibly swollen—for example, an optic nerve glioma—or inapparent in the intact brain if a deep structure is involved. In the latter instance, transverse section often reveals a grayish white area that subtly obliterates normal structure. This is often better appreciated in stained sections (H&E, Luxol fast blue) than in the gross specimen. Swelling of the affected hemisphere with displacement of the midline away from the neoplasm is often a clue. Secondary effects, such as edema, may produce herniations at sites removed from the primary astrocytoma. In contrast, progressively more anaplastic (malignant) astrocytomas are more clearly delineated and are often mottled reddish yellow with areas of hemorrhage and necrosis. Such tumors are readily identified by CT and MRI (with enhancement) or technetium-99 isotope uptake because of severe disturbances of the blood-brain barrier. Evidence of immune responsiveness may be seen at the tumor margins in the form of perivascular cuffs of lymphocytes. Whether the presence of such cells is a favorable prognostic indicator is controversial. The mass effect of the tumor also results in vasogenic edema and a reactive astrogliosis at its perimeter.

Several cytological patterns of human astrocytomas are recognized, and some are represented in the astrocytomas of animals. Astrocytomas may be derived from fibrillary or protoplasmic astrocytes; **fibrillary astrocytomas** account for the majority. The cytological subtype influences the gross appearance of the tumor. When the cytoplasm is packed with glial fibrils, the tumor is firm and resilient. In contrast, **protoplasmic astrocytomas** tend to be soft and gelatinous, consisting of smaller, stellate cells with roundish nuclei, few processes, and are often punctuated by microcystic areas. In some fibrillary astrocytomas, the neoplastic cells grow as bundles of spindly, bipolar cells and are described as **pilocytic** or **piloid** (meaning "hairlike"). **Gemistocytic astrocytomas** are characterized by large cells with abundant eosinophilic cytoplasm and a marginally located nucleus or multiple nuclei. In **astroblastomas**, some of which may arise from tanycytes,³ cells are radially arranged around

blood vessels (pseudorosettes),^{4,5} a pattern seen also in ependymoma and papillary meningioma.

Malignant astrocytomas are identified microscopically by their nuclear pleomorphism, the presence of mitotic figures (sometimes atypical) and small cells with dense, hyperchromatic nuclei. Further regressive changes are areas of necrosis, vascular proliferation (often in the form of "glomeruloid" nests, so named because they resemble the vascular tuft of the nephron), and bizarre, multinucleated giant cells. Interestingly, the large, multinucleated cells, although worrisome, are biologically irrelevant; their presence in human glioblastomas indicates a better prognosis than in cases of glioblastoma multiforme in which they are lacking.⁶ The factor or factors that induce the abundant endothelial cell hyperplasia in glioblastoma are uncertain, but roles for both renin (produced by the neoplastic astrocytes)⁷ and platelet-derived growth factor (produced in part by the tumor cells and in part by the vascular endothelium)⁸ have been proposed.

Classification of human astrocytomas is of considerable importance for prognosis and appropriate management of the patient. Such a consideration has not, to this time, become relevant in veterinary medicine. In a few animal medical centers, treatment of canine and feline brain tumors by surgery, irradiation, and chemotherapy is now attempted.^{9,10} However, the recognition of the wide spectrum of spontaneous gliomas, particularly in the dog, may encourage our colleagues in human neuro-oncology to use such cases for studies of tumor imaging and experimental therapies.

Several **classification schemes** have been applied to human astrocytomas, including Kernohan's classical system of grading in which a grade 1 astrocytoma is the most benign ("low grade") and grade 4 the most malignant ("high grade"); subsequent proposals have attempted to make the grading process less subjective and more reproducible.¹¹ Others employ a three-tiered system¹² in which the groups are designated **astrocytoma**, **anaplastic astrocytoma**, and **glioblastoma multiforme** (Table 6-1). More recently, astrocytomas of various grades have been related to their derivation from type 1 or type 2 astrocytes, which also may be prognostically valuable.¹³ Although the use of a classification scheme for animal astrocytomas is an academic exercise at this time, if a grading is given, we prefer the three-tiered system of Burger and co-workers.¹² The histological features that assign a tumor to a group include tumor cellularity (density), degree of pleomorphism, presence of vascular proliferation, mitotic figures, and necrosis.¹⁴ Necrosis seems to be a particularly bad prognostic feature. **Glioblastoma multiforme** is equated with the highest-grade astrocytoma by many neuropathologists and is thought to evolve within a pre-existing astrocytoma over the course of time. Thus malignant gliomas should be viewed as heterogeneous populations of neoplastic cells that may progress through the selection of subpopulations in the pool.¹⁵ Microscopic features of glioblastoma multiforme in-

Table 6-1. Classification of astrocytic tumors

| Criteria | Astrocytoma | Anaplastic astrocytoma | Glioblastoma multiforme |
|------------------------|--------------|------------------------|-------------------------|
| Hypercellularity | Slight | Moderate | Moderate to marked |
| Pleomorphism | Slight | Moderate | Moderate to marked |
| Mitosis | None or rare | Present | Present |
| Vascular proliferation | None | Present | Present |
| Necrosis | None | None | Present |

Adapted from Burger PC, Vogel FS, Green SB, et al: Glioblastoma multiforme and anaplastic astrocytoma: pathologic criteria and prognostic implications, *Cancer* 56:1106-1111, 1985; and Fuling KH, Nelson JS: Cerebral astrocytic neoplasms in the adult: contribution of histologic examination to the assessment of prognosis; *Semin Diagn Pathol* 1:152-163, 1984.

clude necrosis with pseudopalisading of cells, abundant vascular proliferation, multinucleated cells, hypercellularity, and anaplasia (Fig. 6-16). Often a conclusive astrocytic origin cannot be established, even by EM or immunocytochemistry. Furthermore, such features are sometimes seen in high-grade oligodendrogliomas and ependymomas,¹⁶ and so a glioblastoma multiforme may be a common end point for one of several malignant glial lines. An older, now less popular view of the glioblastoma is that they are primary tumors, arising not by dedifferentiation within an existing glioma, but from an embryonal cell. Many gliomas are mixed (oligodendroglioma-astrocytoma), perhaps reflecting an origin from a bipotential progenitor cell.¹⁷

A further consideration in assigning a grade to a glioma is that their morphology may vary from area to area. Examination of a small fragment may lead to erroneous diagnosis; such is the problem of human surgical pathology in cases where the tumor is largely inaccessible to the neurosurgeon or involves a vital structure and so cannot be totally removed.¹⁸ In veterinary medicine we invariably have the luxury of examining the whole neoplasm.

Malignant astrocytomas may spread by subpial or perivascular extension, along white matter tracts or by way of the ventricles and CSF pathways. However, primary leptomeningeal astrocytomas are recognized in humans,¹⁹ presumably derived from heterotopic glial rests. Other variants sporadically seen in animals are **gliomatosis cerebri**, wherein cells infiltrate diffusely but fail to form a discrete primary mass, and **gliosarcomas**, in which a primary glioma (most commonly an astrocytoma) incites neoplastic change in the immediate mesenchymal stroma. In the latter group, a case has been made that some of the mesenchymal component is derived from vascular endothelium.²⁰ Any astro-

cytoma that invades the leptomeninges may incite a scarious (fibroblastic) response.

In humans, **granular cell astrocytomas** are described with transitional forms between pure granular cells and astrocytic cells.^{21,22} **Pleomorphic xanthoastrocytomas** are lipidized astroglial tumors seen in young patients, often with a relatively long survival time.^{23,24} These and other variants²⁵ await description in animals.

Numerous electron microscopic and immunocytochemical studies of various human astrocytomas have been reported. Ultrastructural features include cytoplasmic glycogen granules and bundles of 10-nm intermediate filaments.²⁶ Immunocytochemical approaches have largely confirmed that the best-differentiated, most benign astrocytomas express most strongly the glial fibrillary acidic protein, which is visualized ultrastructurally as the cytofilaments. Coexpression of GFAP and vimentin in astrocytomas has been demonstrated.²⁷

In animals, neuroectodermal tumors are most common in **dogs**. A predilection for the brachycephalic breeds has been recognized for many years and, in particular, the Boxer and Boston Terrier. In our experience, astrocytomas comprise the majority of canine gliomas, an observation not shared by our European colleagues (see the section on the oligodendroglioma). Despite a predilection for the brachycephalic breeds, we have encountered astrocytomas in numerous and varied dog breeds. No sex preference is noted, and patients are in the "mature to aged" category. They occur most commonly in the cerebrum and diencephalon, presenting with behavioral changes and seizures, and sporadically in the cerebellum and spinal cord.²⁸ Tumors of the caudate nucleus and internal capsule area may be derived from the subependymal plate.² Grossly, canine astrocytomas vary from vague infiltrative gray-white masses to more clearly delineated hemorrhagic and necrotic tumors characteristic of glioblastomas (Figs. 6-17 and 6-18). So-called "butterfly" tumors, which may cross from one hemisphere to the other by way of the corpus callosum, appear not to be recognized in canine glioblastomas. We have observed cystic cerebellar astrocytomas, a common feature of this variant in humans. Microscopic features are consistent with fibrillary, protoplasmic, pilocytic, and gemistocytic types.^{29,30} Mixed tumors, most often of astrocytoma with oligodendroglioma, are also encountered.³¹ In glioblastomas, necrosis (Fig. 6-19) with pseudopalisading and glomerular vascular proliferations are common; sometimes there are long ribbons of endothelial cells. Tumor cells are fusiform with small, sometimes hyperchromatic nuclei. Some canine astrocytomas are anaplastic (Fig. 6-20, A), but the extremes of nuclear pleomorphism with exuberant multinucleated forms, seen in human and primate glioblastomas, are much less common.² The canine variant often qualifies as a small-cell glioblastoma. At the margins of these (and other masses), reactive astrocytes must be differentiated from the neoplastic population. Well-differentiated canine astrocy-

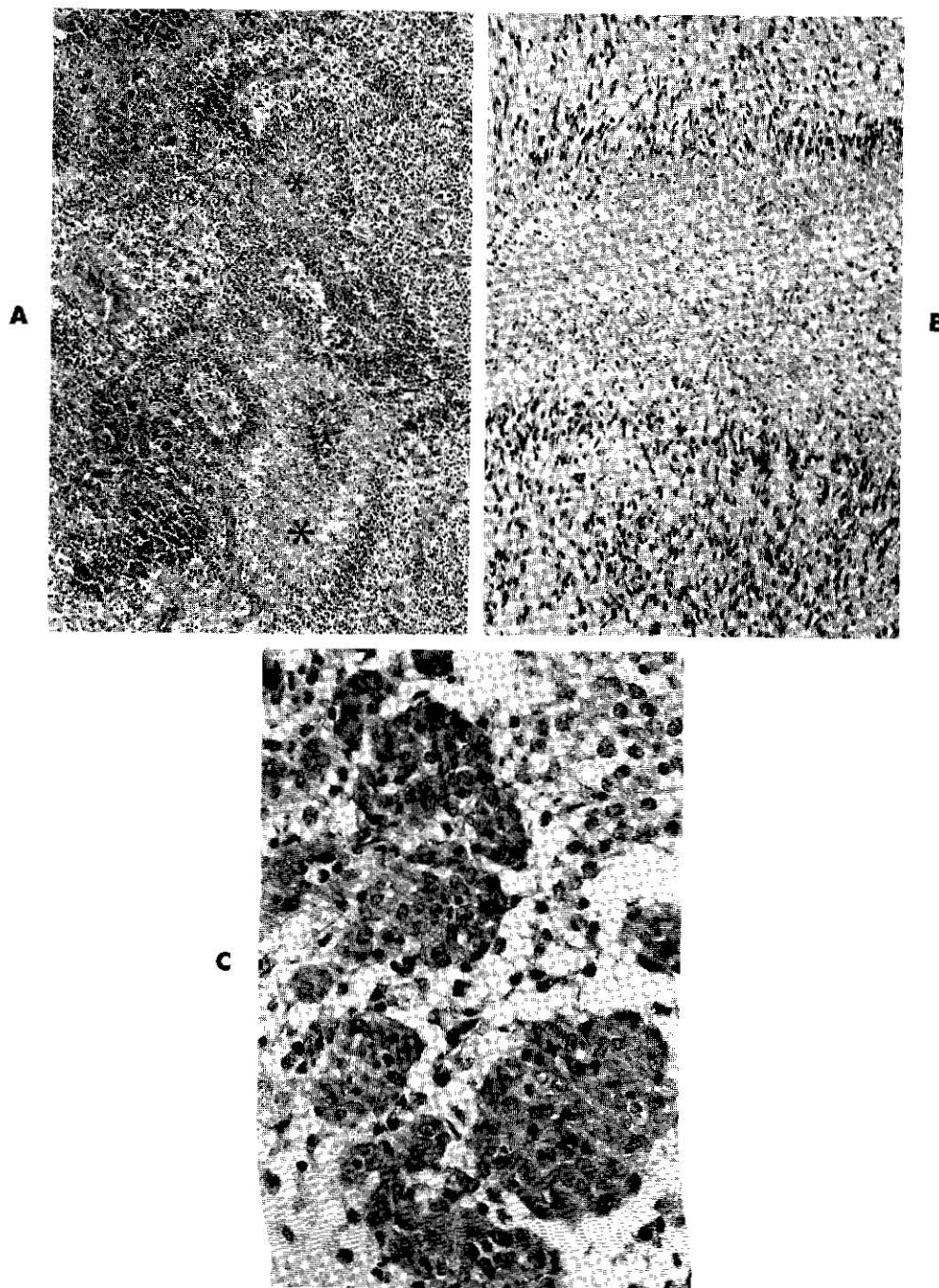


Fig. 6-16. Glioblastoma in three dogs. **A**, Necrosis (*asterisks*) and pseudopalisading. (H&E, $\times 90$.) **B**, Pseudopalisading adjacent to area of necrosis. (H&E, $\times 180$.) **C**, Glomeruloid vascular proliferation. (H&E, $\times 350$.)

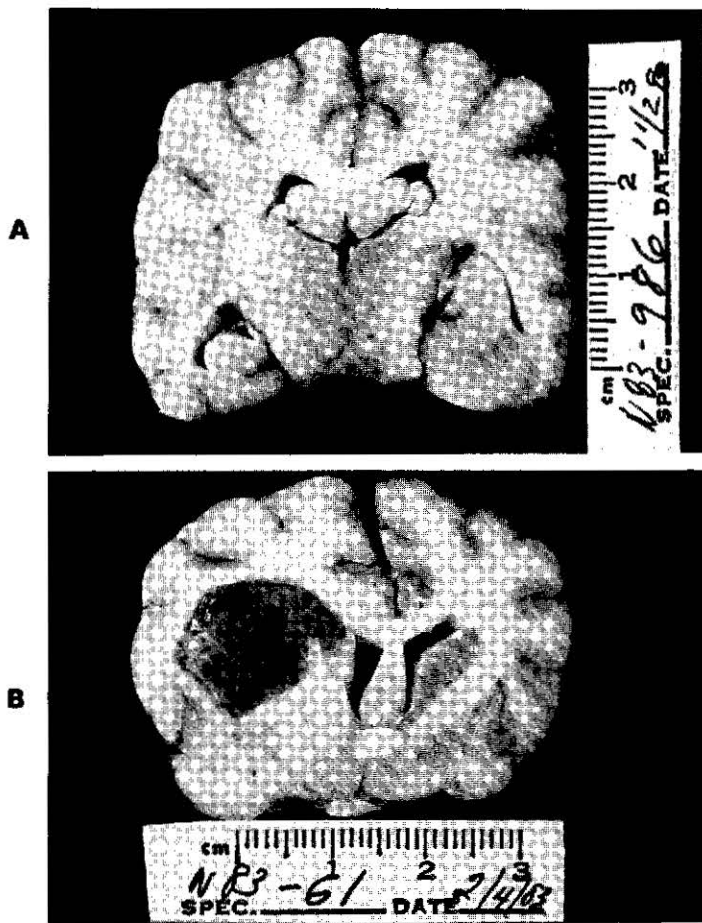


Fig. 6-17. Astrocytoma, dog. A, Low-grade tumor infiltrates pyriform lobe, parahippocampal gyrus and hippocampus. B, Glioblastoma multiforme: Soft, hemorrhagic, sharply demarcated mass replaces centrum semiovale and caudate nucleus.

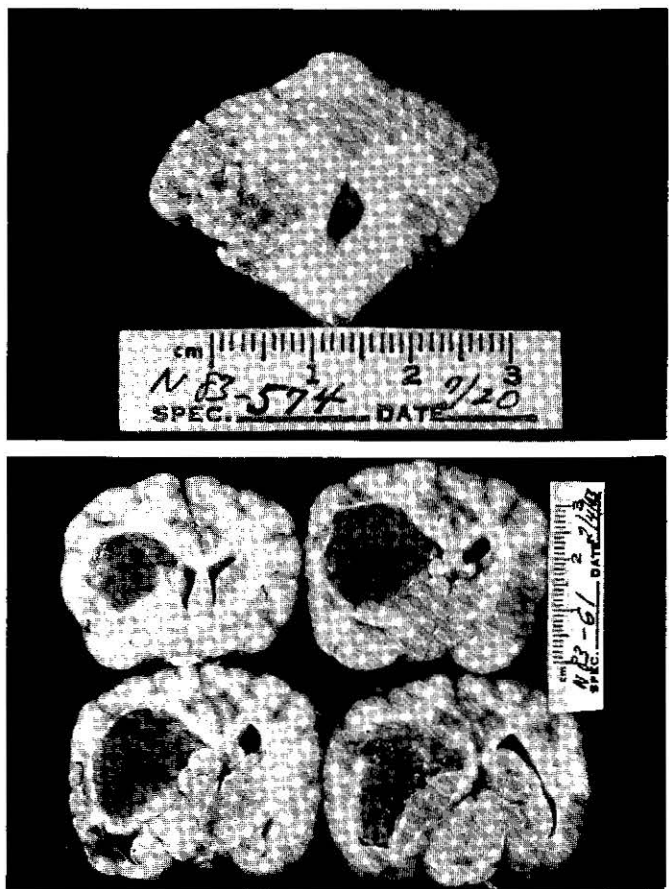


Fig. 6-18. Astrocytoma, dog. A, Cystic astrocytoma, cerebellum. B, Glioblastoma, same dog as Fig. 6-17B.

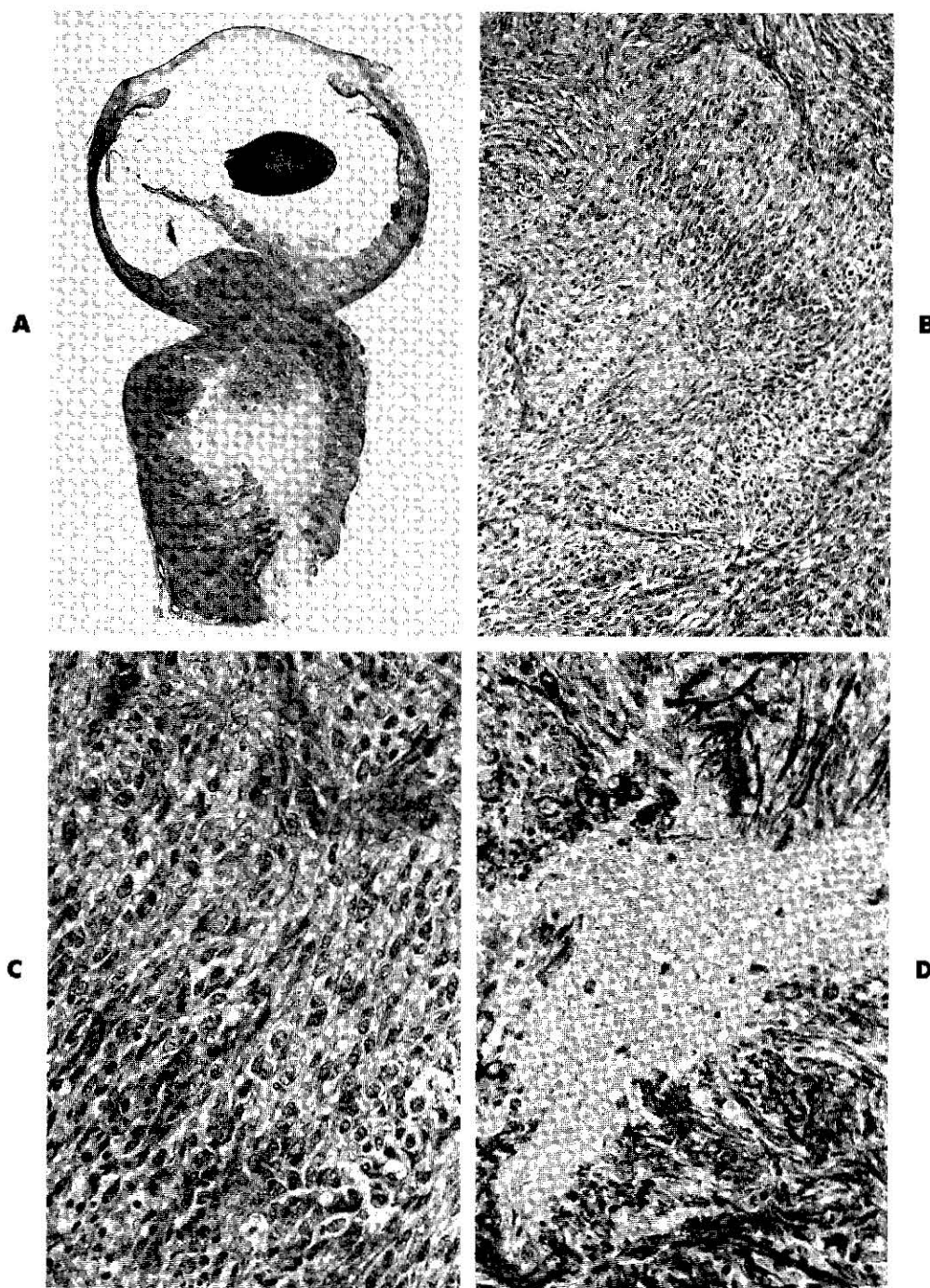


Fig. 6-19. Optic nerve glioblastoma, dog. **A**, Tumor massively expands the optic nerve and infiltrates the posterior uvea. (H&E, $\times 3$.) **B**, Microscopic detail at low power: central area of necrosis. (H&E, $\times 140$.) **C**, Detail of spindly cells. (H&E, $\times 350$.) **D**, GFAP immunocytochemistry reveals filaments disposed about an area of necrosis. ($\times 350$.)

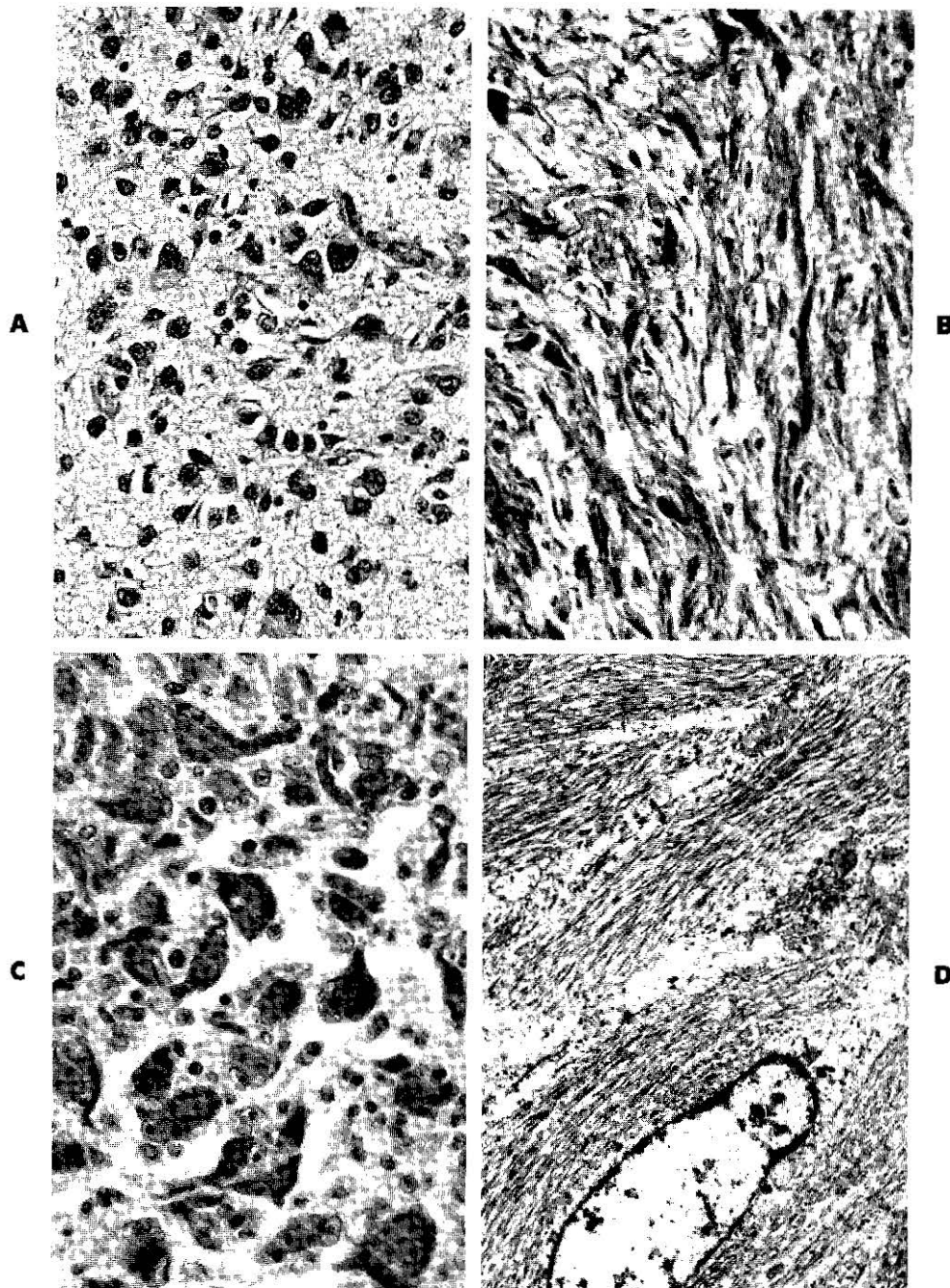


Fig. 6-20. Astrocytoma, dog. **A**, Anaplastic astrocytoma. (H&E, $\times 350$.) **B**, Low-grade fibrillary astrocytoma. (GFAP immunocytochemistry, $\times 350$.) **C**, Gemistocytic astrocytoma, cerebellum. (GFAP $\times 560$.) **D**, Electron microscopic detail of filament-rich astrocytoma, same dog as **C**. ($\times 7575$.)

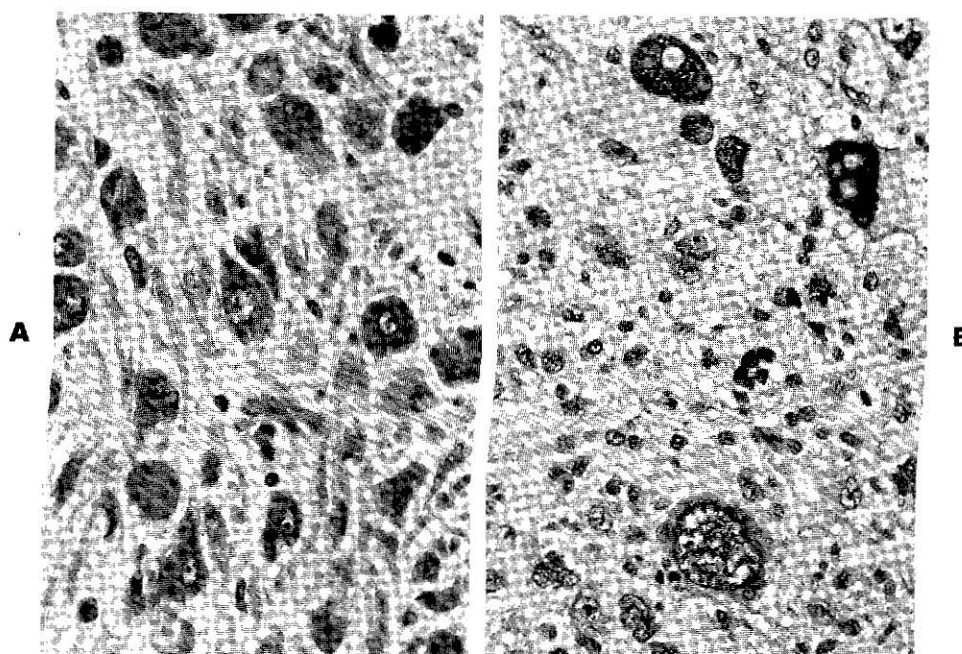


Fig. 6-21. Astrocytoma. **A**, Gemistocytic astrocytoma, spinal cord, cat. (Vimentin immunocytochemistry, $\times 560$.) **B**, Extreme pleomorphism in glioblastoma, baboon. Some giant cells have cytoplasmic invaginations into the nucleus. (H&E, $\times 350$.)

show strong staining for GFAP (Fig. 6-20, *B* and *C*). This feature may be focal or enhanced in certain areas, for example, around blood vessels. If the ultrastructure of these tumors is examined, tumor cells laden throughout the cytoplasm with filaments will be found in cases that are strongly positive for GFAP (Fig. 6-20, *D*). Primitive desmosomal junctions between cell processes may be observed. The nuclei are open-faced with little heterochromatin.

Astrocytomas are uncommon in **cats** but are reported (Fig. 6-21, *A*);³² in this species, meningioma and lymphoma account for most CNS neoplasia. Some feline examples show an astroblastic pattern.³³ In the other domestic species, they are rarely reported; one in the **pig** has been noted.³⁴ Frickhauser and colleagues²⁸ comment that glioblastomas have been found fairly often in cattle, dogs, and pigs, but, certainly for large animals, this has not been our experience. Glioblastoma multiforme has been reported in a **baboon**,³⁵ one of the very few reports of spontaneous brain tumors in nonhuman primates; we have seen a single case (Fig. 6-21, *B*).

Astrocytomas are rare in common **mice** breeds,³⁶ but an incidence of approximately 1% is seen in the VM strain, derivatives of VM, and in the BRVR strain.^{37,38} They are twice as common in males as in females and more often than not are subclinical. No area of predilection within the brain is apparent, but growth in heavily myelinated tracts (corpus callosum, internal capsule, optic tract) is common. Their morphology is usually undifferentiated. A transplantable murine astrocytoma, derived from a mouse of the VM

strain, has been described and characterized.³⁹ Astrocytomas occur at low frequency in **rats** and are described in Wistar and Sprague-Dawley strains.^{40,41} A predilection for periventricular areas has been noted. Mixed astrocytoma-oligodendrogliomas are also recognized with diffuse intermingling of cell types or separate areas of predominantly one cell type or the other. Astrocytomas in rats were said to be consistently GFAP-negative,⁴⁰ which is surprising, to say the least.

The paucity of reports would suggest that gliomas of any variety are uncommon in the avian species. In domestic poultry a **fowl glioma** has been described⁴¹ as an astrocytic tumor, as a glioblastoma, as a mixed gliomatous-mesenchymal tumor,² and as disseminated focal gliomatosis.⁴² To muddy the waters further, this tumor is often seen in a background of disseminated nonsuppurative inflammation; according to Jackson,⁴³ glioma arise in preexisting encephalitic foci. Whether this actually represents a dense inflammatory response to a glial tumor or an exuberant reactive gliosis in a setting of chronic encephalitis is not resolved. Grossly the lesion may be focal or multifocal and nodular. Microscopic lesions are found in the cerebral hemispheres, optic chiasm, brain stem, and cerebellum. Nodules are often subventricular. Some affected fowl have had toxoplasmosis, and a parasitic etiology has been suggested. We have observed a mixed astrocytoma-oligodendroglioma in an 18-month-old Macaw from South America. A yellowish mass occupied the right cerebrum and diencephalon. Microscopically the cells were quite pleomorphic with a giant

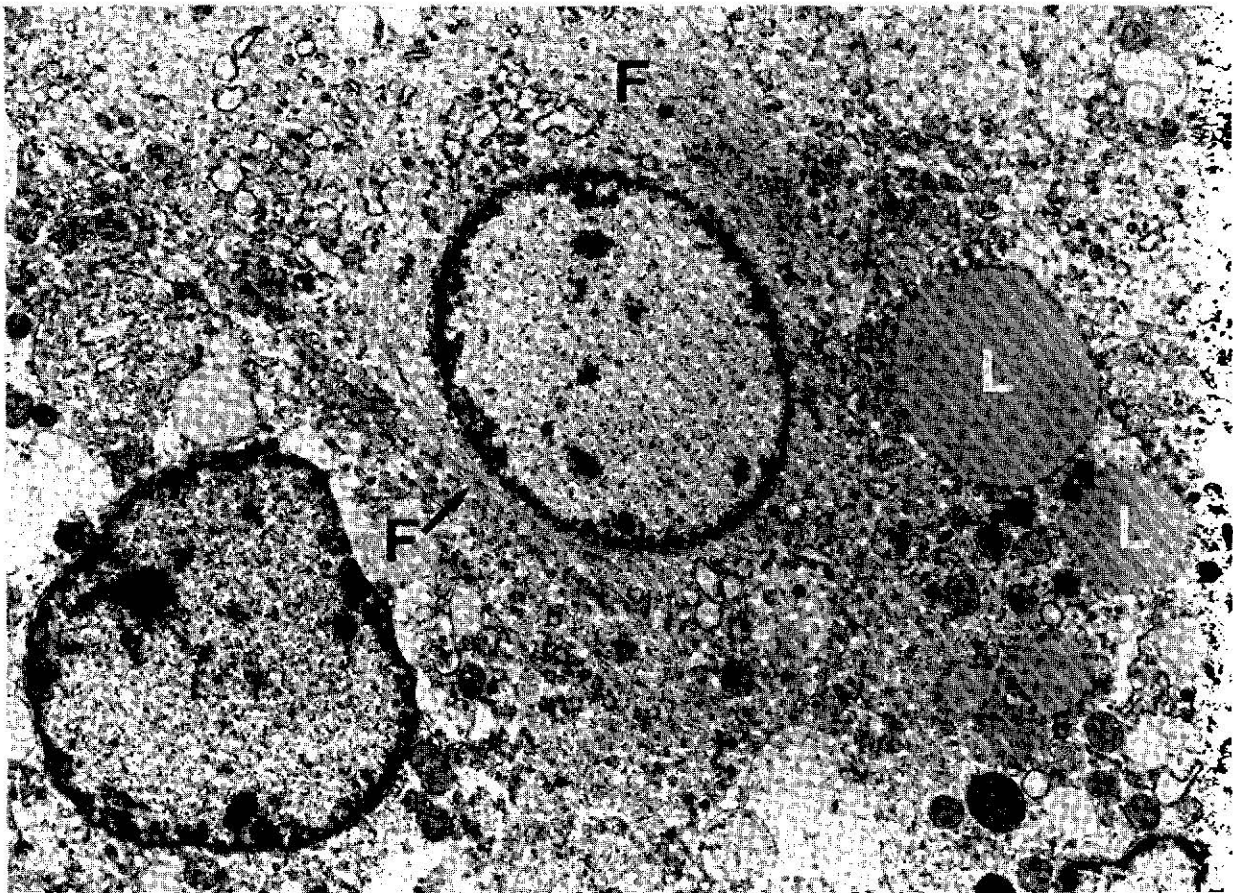


Fig. 6-22. Xanthoglioma, cerebrum, parrot. Notice lipid droplets (*L*) and bundles of astroglial filaments (*F*). ($\times 9350$.)

cell component. Lipidization of neoplastic cells was a conspicuous feature, evident on frozen section and ultrastructurally (Fig. 6-22).

References are on page 397.

OLIGODENDROGLIAL TUMORS

As for other neuroectodermal tumors of animals, **oligodendrogliomas** are most common in the dog. Our Swiss colleagues have found the oligodendroglioma to be the most common canine neuroectodermal tumor.^{1,2} In contrast, our experience at Cornell is decidedly that they are less frequent than the astrocytoma; Moulton³ and McGrath⁴ concur. This discrepancy most likely reflects the large number of Boxers, Boston Terriers, and Bulldogs (breeds with a predilection for oligodendrogliomas) in the Swiss series. Such breeds (with oligodendrogliomas) are certainly seen in the United States,⁵ but perhaps they represent a relatively smaller proportion of the total canine population in this country.

Oligodendrogliomas occur in mature dogs (older than 5 years) and twice as often in males as females.¹ The neurological disorder reflects damage to the prosencephalon with various combinations of depression, change in tem-

perament, propulsive gait, blindness, and seizures. Most oligodendrogliomas are located in white matter of the cerebral hemispheres or the diencephalon. Any part of the cerebrum may be the site, particularly the frontal lobe. In brachycephalic dog breeds, they appear to arise within remnants of the germinal matrix adjacent to the lateral ventricle. Grossly, these tumors are pinkish to gray and often soft and gelatinous (Fig. 6-23). Large tumors (3 cm or more in diameter) show areas of central cystic change. The margins may blend imperceptibly into normal parenchyma or may be relatively sharp. Focal extension into the overlying leptomeninges or deep into the ventricle is common. Microscopically, well-differentiated oligodendrogliomas have a very characteristic honeycomb or fried egg appearance due to artifactual cell swelling producing perinuclear halos (Fig. 6-24). Typically one sees sheets of uniformly small, round, chromatin-rich nuclei with clear, poorly stained cytoplasm and sharp cellular boundaries. Cell processes are inconspicuous. Other features are small, multifocal areas of mineralization and a rich capillary vasculature. These blood vessels branch sharply, a feature nicely demonstrated in reticulin preparations. This feature, recorded in the canine

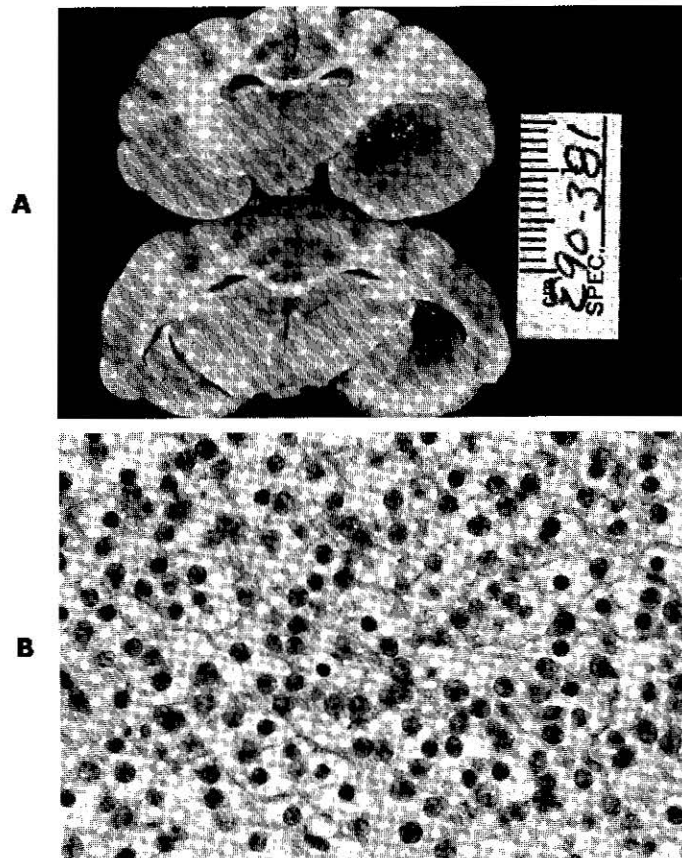


Fig. 6-23. Oligodendroglioma, cat. **A**, Mucoid mass replaces amygdala. **B**, Tumor cells have central or paracentral nuclei and clear cytoplasm. (H&E, $\times 560$.)

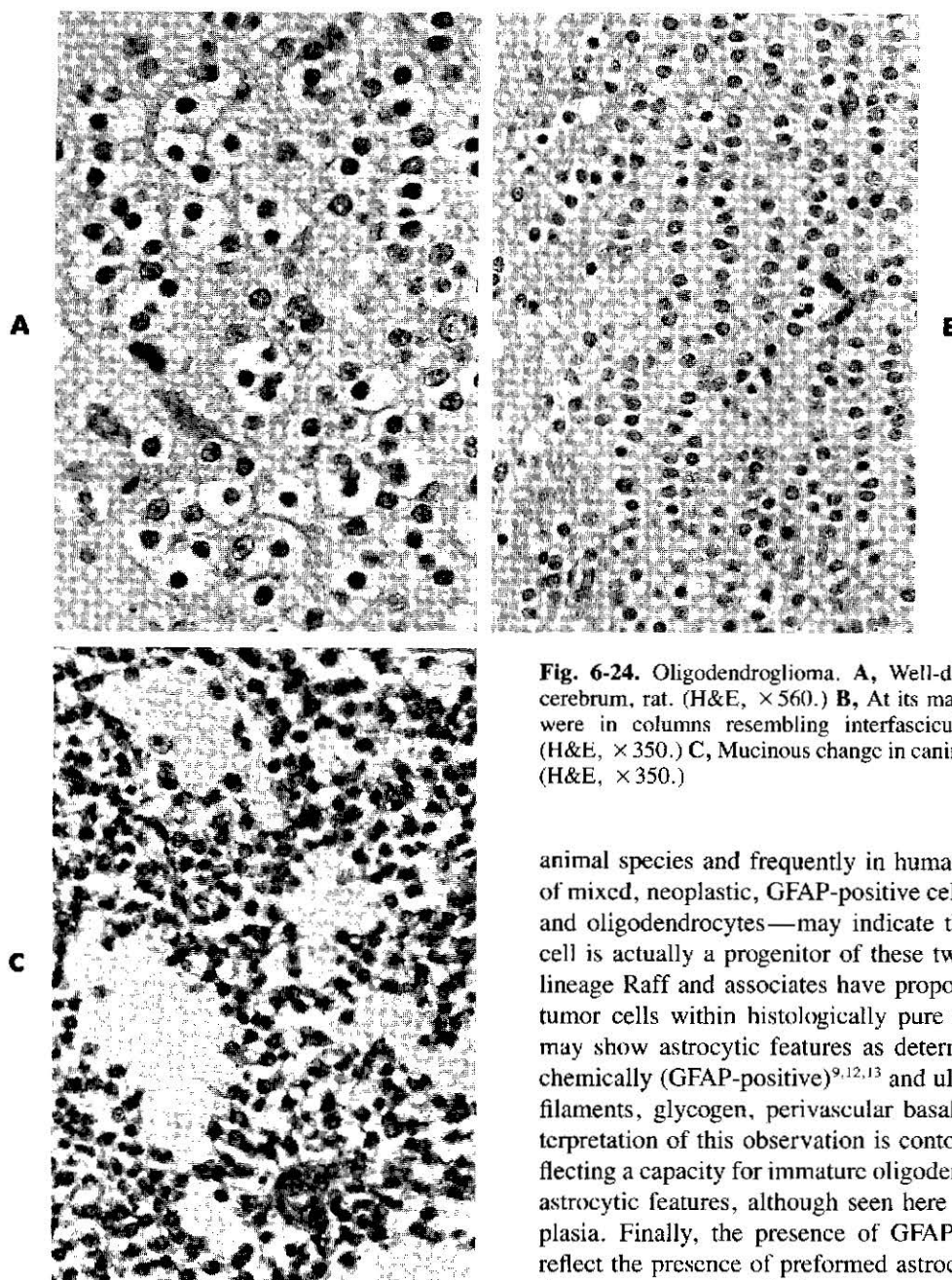


Fig. 6-24. Oligodendroglioma. **A**, Well-differentiated tumor in cerebrum, rat. (H&E, $\times 560$.) **B**, At its margins, neoplastic cells were in columns resembling interfascicular oligodendrocytes. (H&E, $\times 350$.) **C**, Mucinous change in canine oligodendroglioma. (H&E, $\times 350$.)

oligodendroglioma,⁷ is also observed in the human tumor. In some oligodendrogliomas, areas of mucinous degeneration are seen (Fig. 6-24, C). A pale, gray-blue mucinous material accumulates between the cells and may form small lakes. At the margins of this tumor, neoplastic cells may be arranged in chains, reminiscent of interfascicular oligodendrocytes. Where gray matter is infiltrated, perivascular cuffing and satellitosis of neurons with neoplastic cells may occur.¹

Many canine oligodendrogliomas are mixed tumors with areas of astrocytic (and even ependymal) differentiation,^{5,8} and this feature is observed in oligodendrogliomas of other

animal species and frequently in humans.^{9,10} The presence of mixed, neoplastic, GFAP-positive cells—both astrocytes and oligodendrocytes—may indicate that the transformed cell is actually a progenitor of these two glial cell lines. A lineage Raff and associates have proposed.¹¹ Furthermore, tumor cells within histologically pure oligodendrogliomas may show astrocytic features as determined immunocytochemically (GFAP-positive)^{9,12,13} and ultrastructurally (glial filaments, glycogen, perivascular basal lamina).¹⁴ The interpretation of this observation is controversial, perhaps reflecting a capacity for immature oligodendrocytes to express astrocytic features, although seen here in a setting of neoplasia. Finally, the presence of GFAP-positive cells may reflect the presence of preformed astrocytes trapped within the mass or reactive gliosis at the tumor margins. Neoplastic oligodendrocytes do not express myelin basic protein in the dog² or in humans.⁹

Anaplastic (malignant) oligodendrogliomas in the dog are marked by frequent mitotic figures and moderate nuclear pleomorphism, with ovoid to fusiform vesicular nuclei (Fig. 6-25). Glomeruloid vascular tufts are present, and occasionally necrosis with pseudopalisading is seen. The latter features raise the diagnosis of glioblastoma multiforme. Some workers, including ourselves, accept the glioblastoma as a high-grade glioma of diverse origin (astroglial, oligodendroglial, or ependymal tissue).¹⁵ Alternatively, one could argue that such a neoplasm is a mixed oligoastrocytoma that contains highly anaplastic astrocytic elements. A simple

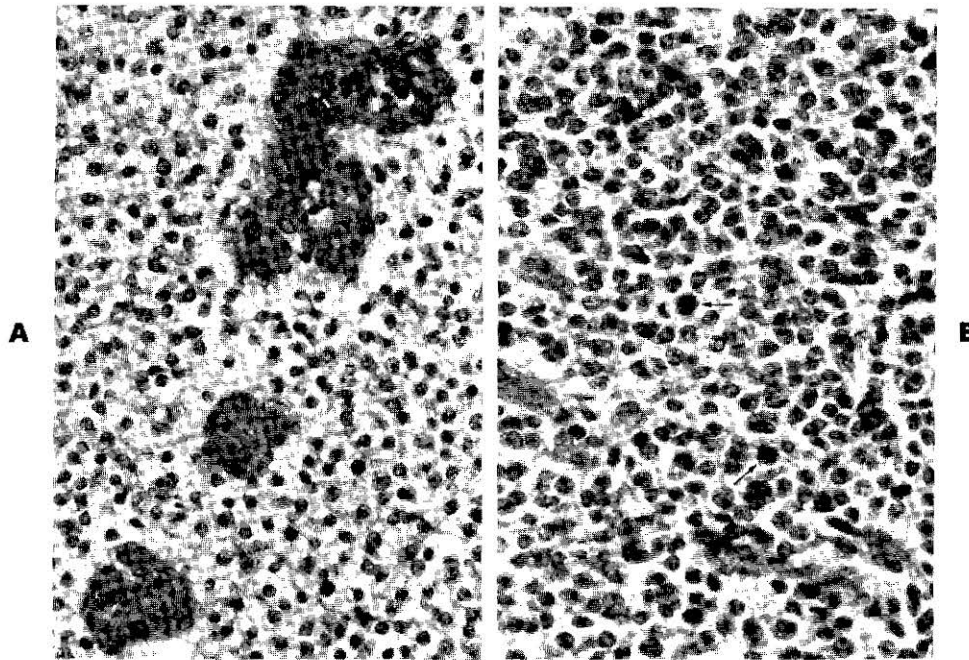


Fig. 6-25. Anaplastic oligodendroglioma, dog. A, Glomeruloid vascular proliferation. (H&E, $\times 350$.) B, Crowded nuclei, mitotic figures (arrows), few honeycomb forms. (H&E, $\times 560$.)

classification system as proposed for human oligodendrogliomas seems the most reasonable to employ in the canine, such as "oligodendroglioma" and "anaplastic oligodendroglioma."¹⁵

Ultrastructural features of canine oligodendrogliomas appear not to have been reported. In humans they are found to be nondescript tumors with few cytoplasmic organelles and an absence of cellular junctions.¹⁶ If a perinuclear halo is present (at light-microscopic examination), the cytoplasm will appear watery by electron microscopy.

Oligodendrogliomas are reported only sporadically in the other domestic and laboratory animal species; they show the same histological features as the canine variant, including mixed astrocytic-oligodendroglial patterns.¹⁷⁻¹⁹

References are on page 397.

CHOROID PLEXUS TUMORS

Tumors of the choroid plexus occur with some frequency in the dog and are also recognized in the horse and cow.¹ They appear to be rare in the other domestic and laboratory animal species. In the dog plexus tumors occur randomly in all breeds without predilection for the brachycephalic breeds.² Canine plexus tumors most commonly arise in the fourth ventricle according to most^{3,5} but not all⁶ authors. They occur less often in the choroid plexuses of the lateral and third ventricles and at these two sites are seen with approximately equal frequency. Zaki and Nafe⁴ described nine cases that were all in male dogs. McGrath⁵ has seen 25 cases, with 16 in males and 9 in females.

Affected animals are typically 6 years of age or older, but cases in younger dogs have been seen. Clinical presentation of fourth-ventricle choroid plexus tumors most commonly reflects an asymmetrical cerebellomedullary mass. Spastic tetraparesis, positional nystagmus, head tilt, and vomiting are common presenting signs,⁴ spanning a course of many weeks or months. Neoplastic cells have not been described in CSF, which may be bloody and contain elevated protein levels. At necropsy, a well-defined reddish to gray, finely nodular extramedullary mass replaces the affected plexus (Fig. 6-26). Obstructive hydrocephalus may be caused by primary or daughter tumors, whereas in humans, hydrocephalus is thought sometimes to result from hypersecretion of CSF by the tumor. Histological examination will reveal a very stereotyped picture of branching papillary structures formed by cuboidal to columnar epithelium with regular, ovoid nuclei supported by a richly vascular connective tissue stroma. Sometimes these tumors have been reported as choroid plexus carcinomas by virtue of their local invasiveness and/or cellular atypia.⁷ This designation is probably better reserved for those few choroid plexus tumors that seed along CSF pathways (Fig. 6-27). In the latter circumstance, small nests and ribbons of papillae are found within the ventricular system and subarachnoid spaces. Extensive spread in the subarachnoid space would qualify as "meningeal carcinomatosis,"^{8,9} which simply describes disseminated growth in the meninges of a primary or secondary carcinoma. In humans, considerable care is taken to rule out the possibility of a metastatic carcinoma

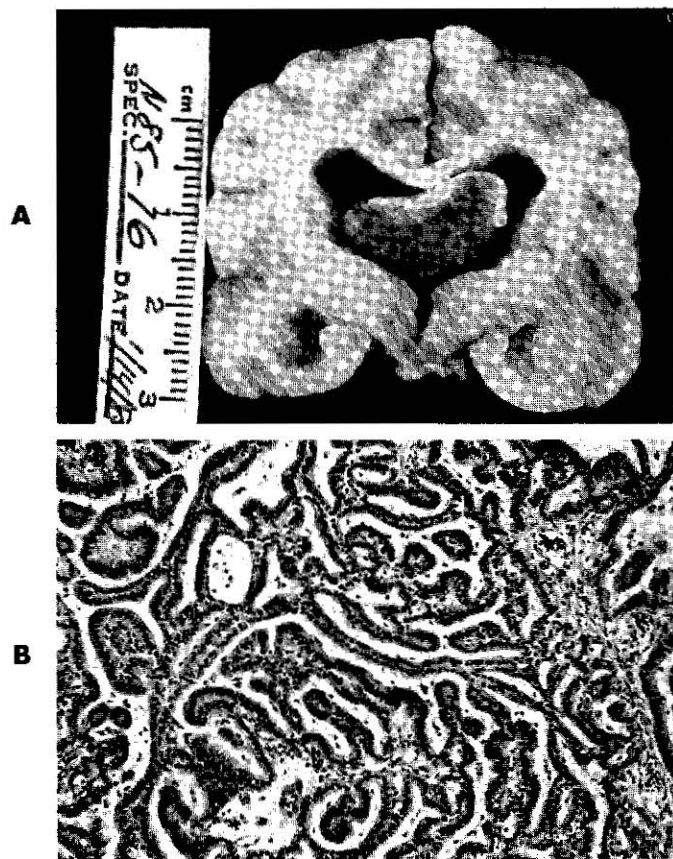


Fig. 6-26. Choroid plexus papilloma, dog. **A**, Papilloma of third ventricle. **B**, Detail of the tumor. (H&E, $\times 140$.)

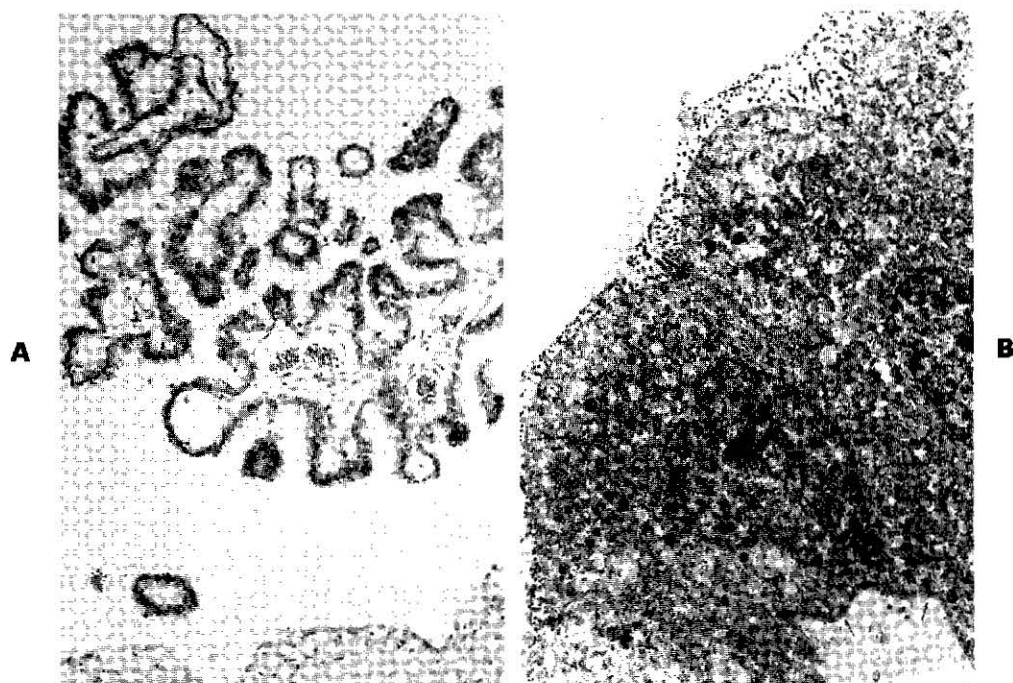


Fig. 6-27. Choroid plexus carcinoma, dog. **A**, Tumor within mesencephalic aqueduct. (H&E, $\times 140$.) **B**, Electron micrograph: Choroid plexus epithelia have surface microvilli and a basal lamina (arrows). ($\times 5500$.)

that has spread to the brain, particularly from lung, breast, or kidney.¹⁰ In the dog, CNS involvement seems to occur with lower frequency from extraneural malignancies, and the differentiation of a primary choroid plexus tumor from a distant carcinoma is rarely a problem, especially so as the investigation is most commonly performed postmortem.

Ultrastructurally, the neoplastic plexus epithelium closely resembles its normal counterpart. In one canine choroid plexus carcinoma studied, neoplastic cells with surface microvilli, basal bodies, and apical tight junctions were observed.⁸ We also have observed similar ultrastructural features in a choroid plexus carcinoma (Fig. 6-27, B). Immunocytochemically, human plexus papillomas are often positive for keratins and sometimes for GFAP.^{11,12} In studies of canine neuroectodermal tumors, all choroid plexus papillomas examined were GFAP-negative,^{6,13} and this has been our limited experience also. A few express cytokeratin.⁶

References are on page 398.

EPENDYMAL TUMORS

Ependymomas are rare in animals. A few have been reported in the dog, and individual cases have been seen in cattle, horses, cats, and rats.¹⁻⁴ Several case reports of an ependymoma at the thoracolumbar junction of young dogs are, in our opinion, a novel extramedullary neoplasm of different cellular origin (see the section on CNS-associated tumors).

Ependymomas are derived from the lining epithelium of the ventricles and spinal cord central canal. Although least rare in the dog, too few have been reported to reveal a site of predilection within the brain. Grossly, ependymomas may be large, infiltrative, and destructive masses and are gray or reddish if hemorrhagic. Eruption from the neuroparenchyma into a ventricular space is common (Fig. 6-28, A), and obstructive hydrocephalus may be a complication. Malignant variants disseminate in the CSF. Microscopically, these are highly cellular, well-vascularized tumors. Tumor cells have ovoid, deeply chromatic, fairly uniform nuclei with indistinct eosinophilic cytoplasm. They grow as solid sheets, except where cuboidal to columnar cells are oriented around thin-walled blood vessels forming pseudorosettes

(Fig. 6-28, B). True rosettes with basally situated nuclei, sharp apical margins, and a central lumen may also be found, although less commonly. Such cells may have surface cilia, and PTAH preparations will demonstrate their basal bodies (blepharoplasts) (Fig. 6-28, C). Mitotic figures are variable in number. In some ependymomas, mucinous change and cyst formation are seen. **Anaplastic (malignant) ependymomas** are marked by moderate nuclear pleomorphism and necrosis and will merge into glioblastoma multiforme.

The human variant, **myxopapillary ependymoma**,^{5,6} occurs at the conus medullaris and filum terminale. The **subependymoma**⁷ is often an incidental observation at autopsy. Neither have been described in animals. The **epen-**

dymoblastoma is a very rare, primitive neuroepithelial tumor with focal ependymal features;^{8,9} one is reported in a dairy calf.¹⁰

Immunocytochemically, classical human ependymomas express vimentin and GFAP but infrequently keratin.^{11,12} In this respect, they show transition toward glial cells in contrast to the epithelial nature of the plexus papilloma, which is keratin-positive and less frequently GFAP-positive. Of nine canine ependymomas stained for GFAP, eight were negative.¹³

Ultrastructurally, human neoplastic ependymal cells show intercellular tight junctions and microvilli that project into a lumen or interdigitate between cells.¹⁴ Cilia and basal bodies may be identified but are less common. Some cells in ependymomas (particularly subependymomas) contain glial filaments. Ependymomas of animals await ultrastructural description.

References are on page 398.

NEURONAL TUMORS

The nomenclature applied to CNS tumors that show neuronal differentiation is confusing. In humans, one group of tumors of small, immature neuronal cells is commonly located within the lateral ventricle and has a relatively good prognosis. These tumors are termed **central neurocytomas** (Fig. 6-29, A).^{1,2} They must be differentiated from **cerebral** or **cerebellar neuroblastomas**,^{3,4} which also could be designated **primitive neuroectodermal tumors (PNET) with neuronal differentiation**.⁵ Although ganglion cells are conventionally thought of as nerve cells located outside the CNS, some central tumors are named **gangliocytomas** or, if the tumors are mixtures, as **ganglioneuroblastomas** or **gangliogliomas**.⁶⁻¹⁰

Neuronal cell CNS tumors are rare. Biologically, they cover a considerable spectrum, from the slowly growing tumors composed of mature nerve cells to the poorly differentiated and malignant neuroblastoma. Gangliocytomas have the features of mature, differentiated nerve cells, that is, vesicular nuclei with a prominent nucleolus, cytoplasmic Nissl bodies, and neuritic processes. Neuroblastomas are characterized by uniform, small, nondescript round cells with central chromatin-rich nuclei and faintly staining cytoplasm.³ They may resemble oligodendrogliomas. Ultrastructural features include the presence of cytoplasmic dense-core neurosecretory granules, microtubules, and synapse-like structures.^{3,11} Neuron-specific enolase and neurofilament proteins are demonstrable by immunocytochemical techniques.^{3,12} There is evidence in humans that neuroblastomas can mature into more highly differentiated forms.¹³

Central nervous system tumors showing nerve cell differentiation are singularly uncommon in animals. **Gangliocytomas** have been described in the dog.^{14,15} They contain ganglion-like cells with multiple processes, a central nucleus, and a nucleolus. A rare cerebellar variant described in a 4.5-year-old horse by Poss and Young¹⁶ resembles its

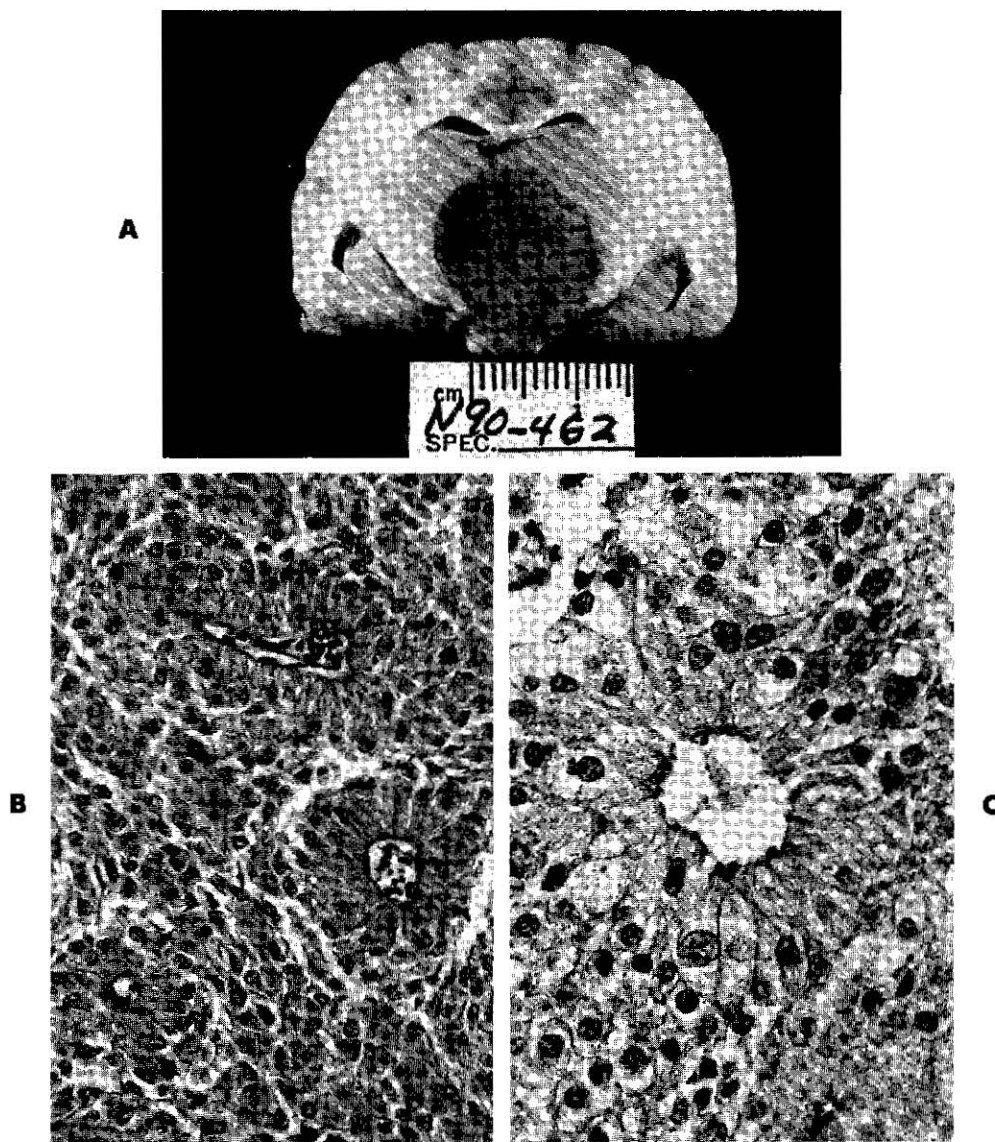


Fig. 6-28. Ependymoma. **A**, Ependymoma of the third ventricle, cat. **B**, Perivascular pseudorosettes in feline ependymoma of lateral ventricle. (H&E, $\times 350$.) **C**, Rosette with apical basal bodies. Ependymoma, dog. (PTAH, $\times 560$.)

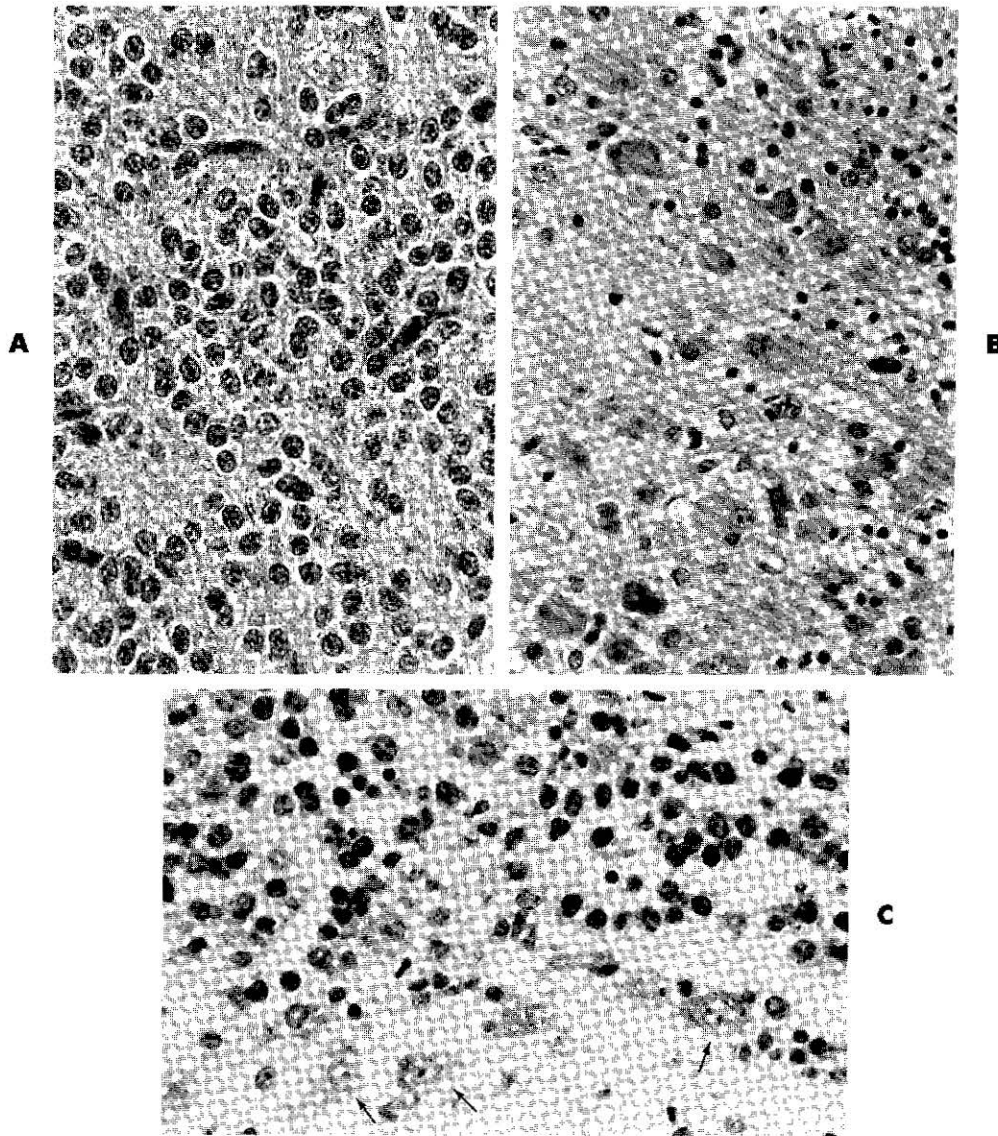


Fig. 6-29. Neuronal tumors. **A**, Intraventricular neurocytoma, human. (H&E, $\times 560$.) **B**, Dysplastic gangliocytoma of cerebellum, human. Granule cell neurons are to the right. (H&E, $\times 350$.) **C**, Ganglioglioma of spinal cord, calf. Ganglion cells indicated by arrows. (H&E, $\times 560$.)

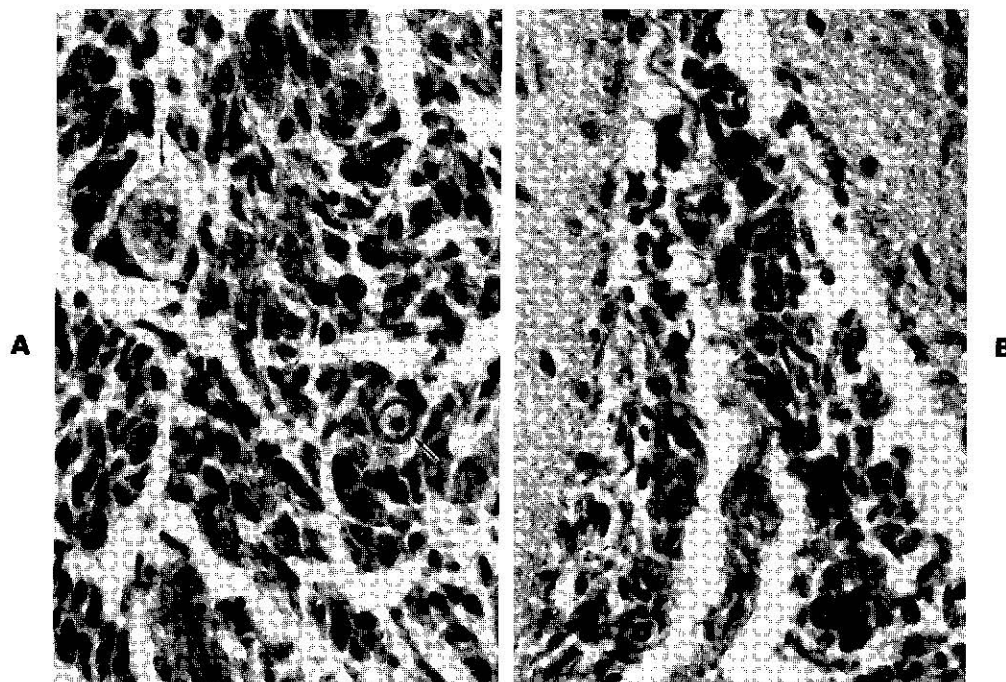


Fig. 6-30. Medulloblastoma, dog. **A**, Tumor with focal neuronal differentiation (*arrows*). (H&E, $\times 350$.) **B**, Tumor invades leptomeninges of cerebellum. (H&E, $\times 560$.)

human counterpart (Lhermitt-Duclos disease) (Fig. 6-29, *B*).¹⁷ Whether this entity represents a malformative or neoplastic process is uncertain, as the designation **dysplastic gangliocytoma** clearly indicates. Roth and co-workers¹⁸ reported a **ganglioglioma**, a neoplasm of ganglion cells and glial cells, in the spinal cord of a 4-month-old calf (Fig. 6-29, *C*).

References are on page 398.

MEDULLOBLASTOMAS AND PRIMITIVE NEUROECTODERMAL TUMORS

Medulloblastomas are common malignant brain tumors of children. They also occur in the young of some animal species, namely, cattle and dogs, and have been observed sporadically in pigs and cats.¹ One is described in a baboon.² Medulloblastomas are almost exclusively located in the cerebellum. They are thought to arise from the external germinal cell layer, which is found below the pia mater during fetal and neonatal life. The medulloblast, for which this entity is named, is actually not an identified cell but is presumed to exist within this population of germinal cells in the developing cerebellum. In children, medulloblastomas are more common in boys than in girls, and most arise from the vermis; they are much less common in adulthood, and in this age group may be located in the cerebellar hemisphere. Such details are not available for examples in animals.

In **calves**, medulloblastomas present in the first few weeks of life with signs of cerebellar disorder.³ Remarkably, Fankhauser and associates observed medulloblastomas in

both of twin calves.⁴ At autopsy a relatively well-circumscribed soft, grayish mass replaces part of the vermis, bulges into the fourth ventricle, and compresses the medulla ventrally and the midbrain rostrally. Hydrocephalus resulting from interference with CSF flow may be observed. Macroscopically these tumors are more infiltrative at their margins than their gross appearance would suggest. They consist of a fairly uniform population that forms sheets of densely packed cells. The nuclei are elongated ("carrot-shaped") and quite dense with heterochromatin. The cytoplasm is pale staining and often inapparent, although an occasional fibrillar process may be seen. Mitotic figures are common. Occasional arrangements of tumor cells form Homer-Wright rosettes, which have a core of pale eosinophilic fibrillary processes.

These tumors show a highly characteristic pattern of subpial extension at their margins, growing as sheets of cells within the molecular and granular layers of the cerebellar cortex. Invasion of the leptomeninges incites a marked fibrous reaction; these are highly malignant tumors, and one should not be surprised to find evidence of dissemination by way of CSF pathways. Medulloblastomas in young **dogs** (Fig. 6-30), **pigs**, and **cats** closely resemble those of calves.

In humans, occasional differentiation along neuronal and glial lineage occurs in medulloblastomas,^{5,6} but this is much less common in animal cases. Human **medullomyeloblastomas** are also recognized, which may contain either smooth or striated muscle admixed within the classical medulloblastomatous elements.

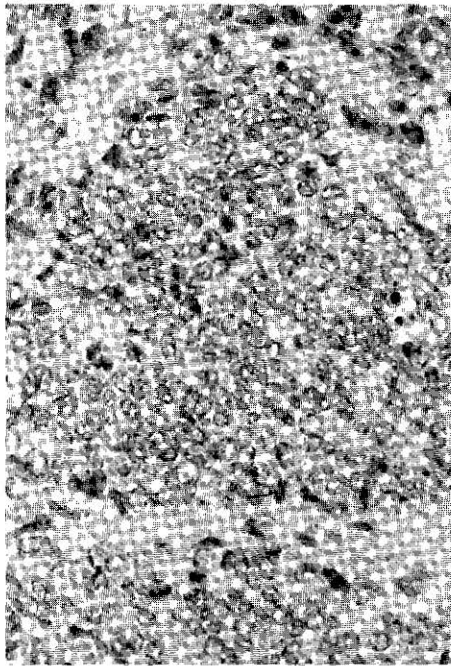


Fig. 6-31. Pineoblastoma, rat. Highly cellular and poorly differentiated tumor. (H&E, $\times 560$.)

There is a considerable controversy in the literature as to the preferred nomenclature of all the primitive neural tumors that are seen in humans (and doubtless occur also in animals). The basis for the argument is the histogenesis and inter-relationships of these tumors. One view is to consider these poorly differentiated tumors as a single group, derived from primitive neuroectodermal cells, and to name them the **primitive neuroectodermal tumors** (PNET). Those that show further differentiation would be so designated, for example, PNET with ependymal differentiation or PNET with neuronal differentiation.^{7,8} On the other hand, the case for retention of the classical terminology and the identification of each as an entity (for example, the medulloblastoma) is strongly argued⁶ on the grounds that important differences in histogenesis and behavior will be obscured if a generic nomenclature is employed.

References are on page 399.

PINEAL TUMORS

In humans, several tumor types arise within or in the immediate vicinity of the pineal gland. These include neoplasms of pineal parenchymal cells and of germ cells (germinoma). In the past, either has been designated pinealoma without clear distinction as to the histogenesis implied.¹ Ganglion cell tumors, chemodectomas, and astrocytic tumors may also arise from the pineal.

Pinealocytic tumors are preferably designated as **pineo-**

cytoma (benign) and **pineoblastoma** (malignant). In animals they are very rare, and Luginbühl and co-workers² are skeptical of many published cases. Fankhauser and associates³ classifies them as "isomorphic" pineal tumors (probably pineocytoma) and "anisomorphic" forms with larger nuclei and pleomorphism (probably pineoblastoma), which in humans are highly malignant. A few pineocytomas have been observed in the **rat**.⁴ These tumors compress but do not invade the adjacent midbrain. They show densely packed cells with round, chromatin-rich nuclei and indistinct cytoplasm. A perivascular pseudorosette or endocrine pattern is observed. Some authors distinguish two cell types in pineal tumors in the rat: large, pale-staining polyhedral cells and fewer, small, intensely eosinophilic cells.^{5,6} Of five pineal tumors seen in Wistar rats,⁵ one would qualify as a pineoblastoma (Fig. 6-31) by virtue of cellular pleomorphism, tumor necrosis, and local invasiveness, and similar features were recorded in a pineoblastoma in a **horse**.⁷ A pineoblastoma in a **cockatiel**, including electron-microscopic study, has been reported;⁸ the ultrastructural features of these tumors in rats are also described.^{5,6}

References are on page 399.

MISCELLANEOUS CENTRAL NERVOUS SYSTEM TUMORS

Primary CNS lymphoma
Microgliomatosis
Gliomatosis cerebri
Polar spongioblastoma
Medulloepithelioma

Primary CNS lymphoma

In animals, CNS lymphomas are most commonly encountered as expressions of multicentric disease, and we have discussed the important forms in the section on metastatic tumors of the CNS. Primary CNS lymphoma is relatively uncommon in humans and rare in animals. In human patients, an association between immunosuppressive disorders and increased frequency of primary lymphoma of the brain is recognized. This is seen with hereditary and acquired immune deficiency states¹ such as drug-induced immune suppression in organ transplant recipients and in patients with acquired immune deficiency syndrome.² Some cases of **reticulosis** in dogs may be examples of primary CNS lymphoma,³ probably of B cell type. They contain mononuclear cells arranged in an angiocentric pattern, predominantly within white matter of the CNS. Their nuclei are ovoid and open-faced with frequent cells in mitosis. (Reticulosis is discussed more fully under granulomatous meningoencephalomyelitis of dogs.) Neoplastic reticulosis is also well recognized in the rat⁴ and has been recorded sporadically in cattle and in horses.⁵

Microgliomatosis

Microgliomatosis of dogs was named for the histologically similar human entity that is now considered by most medical neuropathologists to be primary CNS lymphoma.^{6,7} Historically, this neoplasm was believed to be derived from the microglial cell of the CNS, and some neuropathologists still hold this view. Because microglia have traditionally been considered to have a mesenchymal origin, microgliomatosis has been classified in veterinary medicine with the reticulososes, proliferative disorder of cells of "reticulo-histiocytic" origin, whether vascular (adventitial or pericytic), leptomeningeal, or parenchymal (microglial).⁸ However, the angiocentric pattern of cellular proliferation, so characteristic of inflammatory and neoplastic reticulosis, is not a feature of canine microgliomatosis.

Microgliomatosis is seen in mature and old dogs with signs of slowly progressive diffuse cerebral disease.⁹ At necropsy, there may be no gross changes detected in the brain, or the white matter may be dull, with gray-white junctions less sharp than normal. Microscopic findings (Fig. 6-32) are of diffuse hypercellularity of white matter tracts in the cerebral hemisphere, brain stem,¹⁰ or cerebellum, with cells in approximately parallel relationship along the course of most axons. Individual cells have ovoid to elongated nuclei, sometimes said to be twisted.³ Most nuclei are darkly basophilic and, in their rod shape, mimic so-called rod-cells (microglia); their cytoplasm is usually inapparent. Some cells have more round to ovoid nuclear profiles and are usually also rich in chromatin but sometimes vesicular. Characteristic patterns of growth are as sheets in the white matter (cerebrum, brain stem, cerebellum) and as subpial masses both in the cerebrum and cerebellum. The latter resemble the extensive infiltration (so-called secondary structures) of medulloblastoma. Sometimes infiltrates extend below the glia limitans and form perivascular sleeves. Microgliomatosis in the dog may present as gliomatosis cerebri (see later in the section) with diffuse involvement in the brain and spinal cord.

Electron-microscopic examination of a case of microgliomatosis in a 4-year-old Boxer dog revealed very primitive glial cells (Fig. 6-32, D). Nuclei were ovoid, sometimes cleaved, with clumped heterochromatin. Cytoplasmic differentiation was minimal with polysomes, some granular endoplasmic reticulum, and an occasional mitochondrion. Because of its undifferentiated nature, possible divergent differentiation,¹¹ and pattern of growth (secondary structures), the question can be raised whether microgliomatosis is a primitive neuroectodermal tumor. A neuroectodermal origin for the microglial cell has been proposed.¹² That these tumors are B-cell lymphomas was not supported by the studies of Vandeveld and associates,³ who examined six cases and found that they did not contain immunoglobulins.

Gliomatosis cerebri

Gliomatosis cerebri is a rare glial neoplasm that infiltrates neuroparenchyma over extensive areas of the neuraxis

but fails to form a primary solid mass. Accordingly, macroscopic examination may suggest the presence of a glioma or nothing more than isomorphic gliosis. The extent of anatomical involvement within a single case (cerebrum, midbrain, brain stem, spinal cord) may be remarkable. Most cases in humans are believed to be astroglial, but oligodendroglial and microglial forms are also recognized.^{11,20} Several cases of diffuse gliomatosis in dogs that were part of an immunocytochemical study²¹ were thought to be examples of microgliomatosis.

Polar spongioblastoma

Polar spongioblastoma is a CNS neoplasm of presumed neuroglial lineage of humans, although the cerebral neuroblastoma may mimic it.¹³ They arise near the third and fourth ventricles and have a characteristic pattern of palisaded, slender, fusiform cells. A few have been observed in dogs¹⁴ but were diverse with respect to age at presentation, architecture, and cellular morphology.

Medulloepithelioma

Medulloepitheliomas are primitive tumors derived from the germinal neuroepithelium (or medullary epithelium) of the neural tube. They form simple tubular and papillary structures lined by a low, columnar epithelium. They are seen early in childhood and are intrinsically multipotential. When occurring in the eye, they are designated **teratoid medulloepithelioma**; these have been seen in the dog¹⁵ and horse.¹⁷⁻¹⁹

References are on page 399.

CENTRAL NERVOUS SYSTEM-ASSOCIATED TUMORS

Pituitary gland tumors

Suprasellar germ cell tumors

Craniopharyngioma

Chordomas

Intradural-extramedullary spinal cord tumors in young dogs

Skeletal tumors

In this section, we briefly discuss selected non-CNS tumors that commonly injure the brain or spinal cord. Pituitary adenomas and carcinomas are the most important members of this group.

Pituitary gland tumors

The **pituitary gland (hypophysis)** consists of the adenohypophysis (pars distalis, intermedia, tuberalis) and the neurohypophysis (pars nervosa). Tumors of the pituitary gland are encountered in the dog, horse, and rat; in other species,¹⁻⁴ they are uncommon or rare. This group of neoplasms has been reviewed by Capen.⁵ In the **dog**, tumors of the **pars distalis** and, less so, the **pars intermedia** are

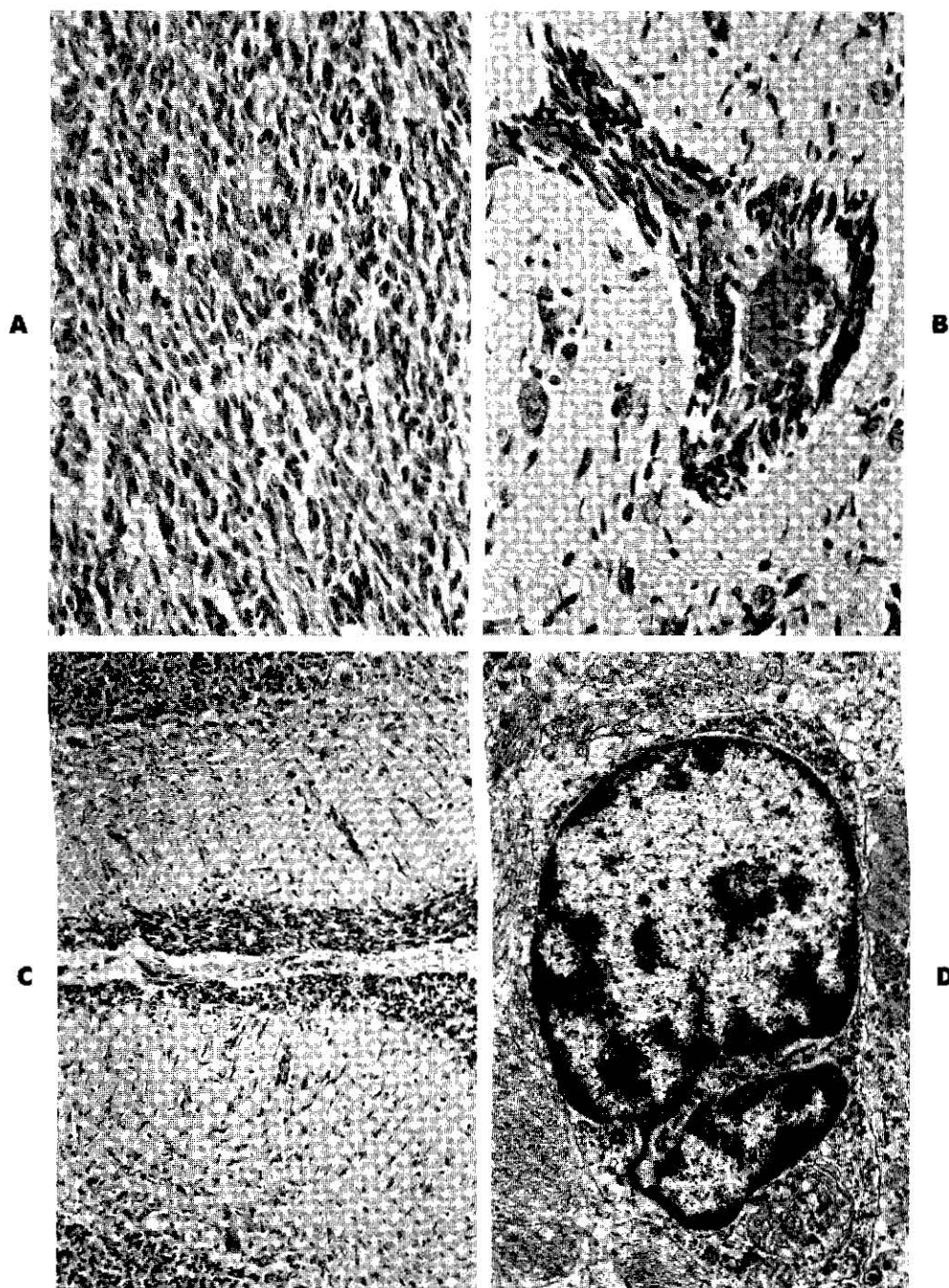


Fig. 6-32. Canine microgliomatosis. **A**, Fusiform neoplastic cells, cerebrum. (H&E, $\times 350$.) **B**, Perivascular infiltrate, cerebrum. (H&E, $\times 350$.) **C**, Invasion below pia and in molecular layer of the cerebellum. (H&E, $\times 140$.) **D**, Ultrastructural detail: deeply invaginated nucleus with peripheral chromatin. Simple cytoplasm contains polysomes and a few mitochondria. ($\times 17,000$.)

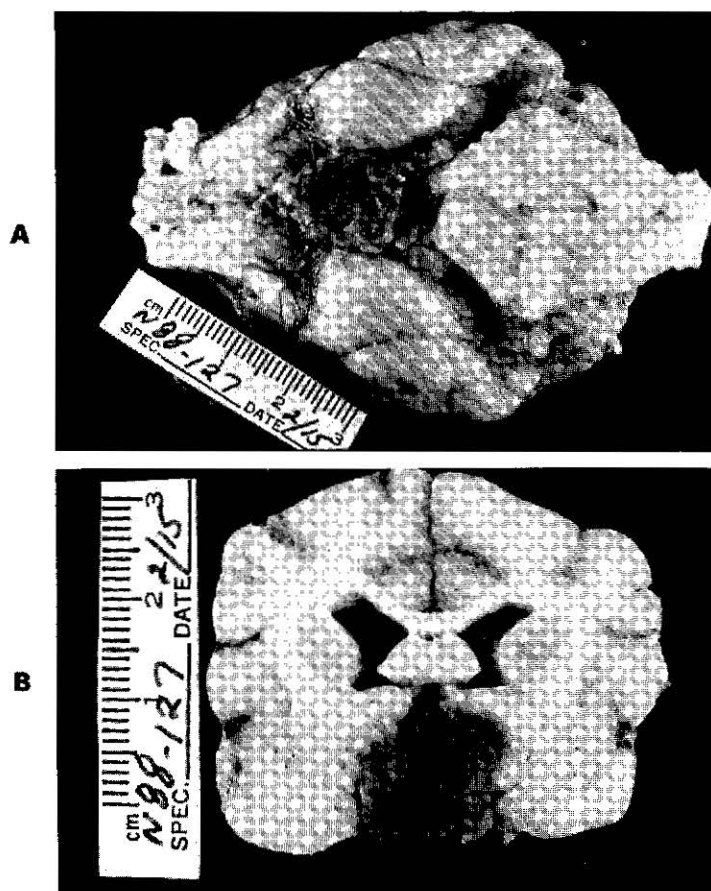


Fig. 6-33. Pituitary tumor, dog. A, Large tumor of pars distalis. B, Extensive compression of diencephalon.

of importance.⁶ Most are classified as adenomas, derived from a distinctive ACTH-producing population of chromophobes, the corticotrophs.⁷ Clinical presentation is often a consequence of their hypersecretion, as many of these tumors are functional. Excessive ACTH production, resulting in pituitary-dependent hyperadrenocorticism, is the most common syndrome⁸ and is manifest by hair loss, mineralization of the skin, abdominal distension, and muscle weakness. The gait may be stiff because of glucocorticoid-induced myopathy.^{9,10} Progressive tumor growth results in destruction of other parts of the hypophysis and ultimately hypothalamic and even thalamic tissue; pituitary tumors expand in the direction of least resistance, which in dogs, horses, and rats is dorsally through the incomplete diaphragma sellae. Diencephalic injury results in a change in sensorium (often lethargy or depression) and sometimes causes circling or head pressing. There may be concomitant diabetes insipidus with excessive thirst and the voiding of copious volumes of urine of low specific gravity. Less commonly, visual defects result from optic chiasm compression.

At necropsy the pituitary is enlarged, sometimes up to 3 or 4 cm in diameter (Fig. 6-33). The tumor is white or

reddish brown from hemorrhage. The largest tumors progressively compress and obliterate the infundibulum, ventral aspects of the third ventricle, hypothalamus and thalamus, and impinge upon the internal capsules and optic tracts. The extent of diencephalic injury is best appreciated in transverse sections of the brain. Microscopically, adenomas of the pars distalis fall into sinusoidal or diffuse patterns (Fig. 6-34, A).⁶ The neoplastic cells are large or small chromophobes (most often the former); they are polyhedral in shape with vesicular nuclei, one or two nucleoli, and abundant finely granular eosinophilic cytoplasm. The sinusoidal pattern contains prominent vascular spaces and a few colloid-filled follicles. The diffuse pattern consists of solid sheets of chromophobes and few vessels. These tumors merge into remnants of the pars distalis and progressively replace the pars nervosa and stalk. Areas of necrosis and mineralization may be found. In contrast, chromophobe tumors derived from the pars intermedia tend to be smaller, are less destructive, and are clearly delineated from the compressed pars distalis. Clusters of chromophobes are found among numerous follicles that contain a PAS-positive colloid. Immunocytochemical studies reveal staining for ACTH, β -lipoprotein:

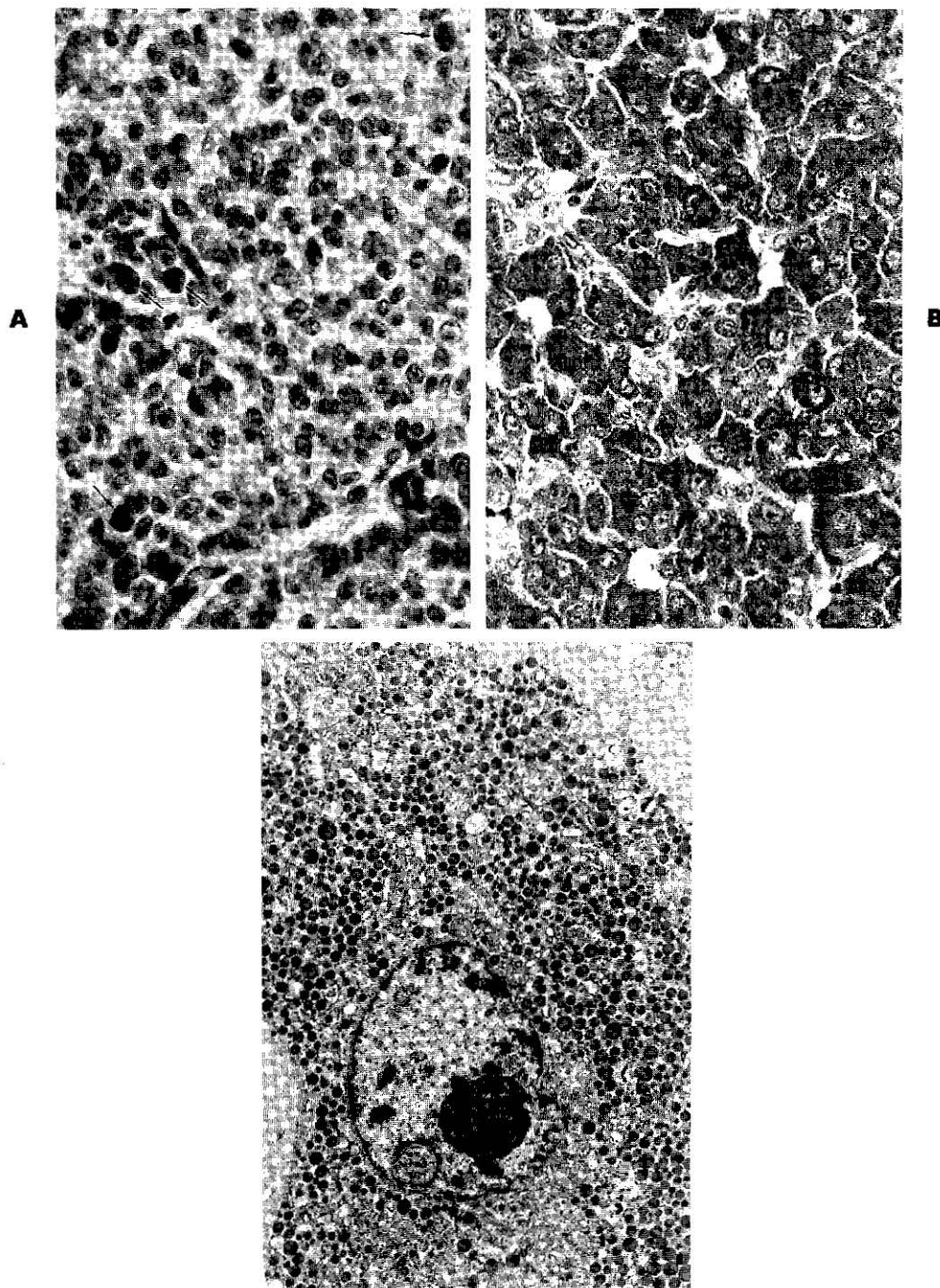


Fig. 6-34. A, Chromophobe adenoma, dog. Solid pattern. Arrows indicate acidophils trapped within the mass. (H&E, $\times 560$.) B, Acidophil adenoma, dog. (H&E, $\times 560$.) C, Acidophil adenoma, cat. Cytoplasm filled with dense secretory granules. ($\times 9100$.)

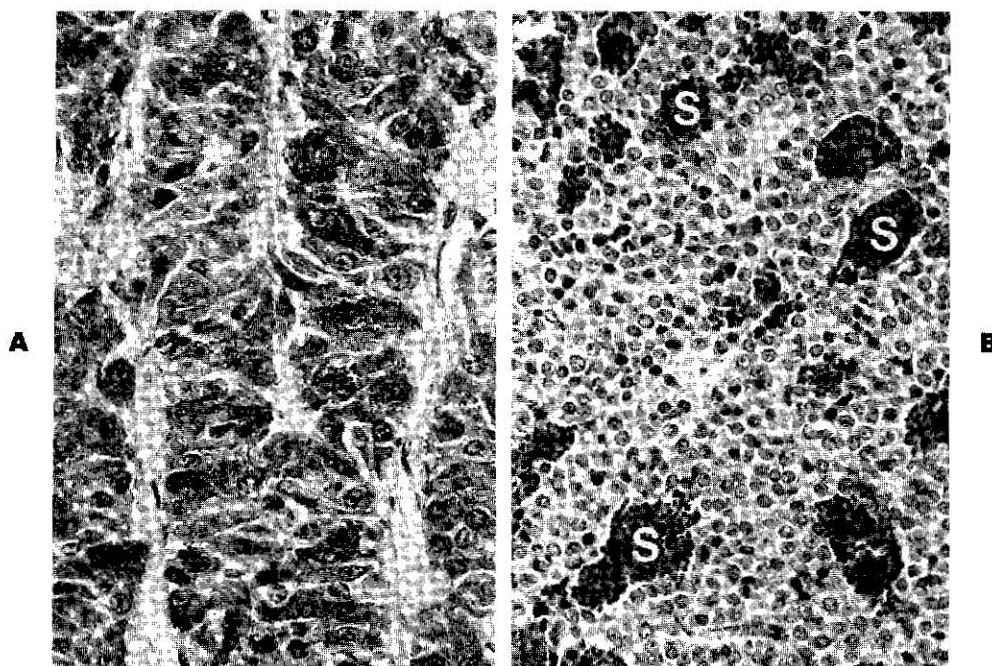


Fig. 6-35. A, ACTH expression in tumor of pars intermedia, horse. (Immunocytochemistry, $\times 560$.) B, Chromophobe adenoma, rat, sinusoidal (S) pattern. (H&E, $\times 350$.)

and β -endorphin in both pars distalis and pars intermedia adenomas of the dog.¹¹ Strong α -melanin stimulating hormone immunoreactivity occurs in pars intermedia tumors. The ultrastructural features of the canine adenohypophyseal chromophobe adenomas have been described.¹² Endoplasmic reticulum, Golgi complexes, and secretory granules are abundant.

Chromophobe carcinomas are much less common. Separation from the adenomas is made on the basis of extensive invasion along the base of the brain, into the sphenoid bone,⁵ and into blood vessels. Nuclear pleomorphism and the mitotic index may be no more marked than in some adenomas.

Compared to the dog, pituitary tumors in the **cat** are encountered infrequently. A syndrome of insulin-resistant diabetes mellitus and acromegaly, resulting from growth hormone-producing acidophil adenomas (Fig. 6-34, C), has been recognized.^{4,13}

Pituitary-dependent hyperadrenocorticism is seen in mature **horses**, often mares, with **adenomas** of the **pars intermedia**. These animals present with a history of weight loss, excessive thirst, chronic infection (sometimes conjunctivitis), and a long, shaggy hair coat.¹⁴⁻¹⁶ Laboratory investigation reveals hyperglycemia, which is insulin-resistant, and glycosuria.¹⁷⁻¹⁹ At necropsy the hypophysis bulges from the sella turcica. A firm, nodular, yellowish gray, somewhat hemorrhagic mass compresses the pars distalis and pars nervosa and may impinge upon the hypothalamus. Microscopically, the tumor is divided into lobules by fine

connective tissue septae. The cells are polyhedral to spindle-shaped with oval, moderately chromatic nuclei and faintly eosinophilic granular cytoplasm, sometimes palisading along vascular stroma. Occasional follicles are formed. Expression of ACTH has been shown immunocytochemically and biochemically within these tumors (Fig. 6-35, A).^{16,20} Pro-opiomelanocortin is also demonstrable, and its derivatives may contribute to the characteristic clinical syndrome in affected horses.^{21,22}

In the aged **rat**, spontaneous tumors of the adenohypophysis are seen in males and females. Most arise from the pars distalis, and many are prolactin producing.^{23,24} Microscopically, sinusoidal (Fig. 6-35, B) and solid patterns of growth are found. Carcinomas that metastasize to the lungs have been observed.

Tumors of the **neurohypophysis** are recognized in humans (pituicytoma, granular cell tumor), but only a couple of **pituicytomas**—tumors of the neurohypophyseal astrocytes (pituicytes)—have been reported^{25,26} in animals.

Suprasellar germ cell tumors

The next group to be discussed is the **suprasellar germ cell tumors**. Tumors of the germinal epithelium are classically associated with the gonads. Extragonadal cases are explained by the presumed ectopic migration of germinal epithelium from the yolk sac and its persistence at these novel sites. Extragonadal germ cell tumors are rare in animals and humans. The intracranial variety occurs at two

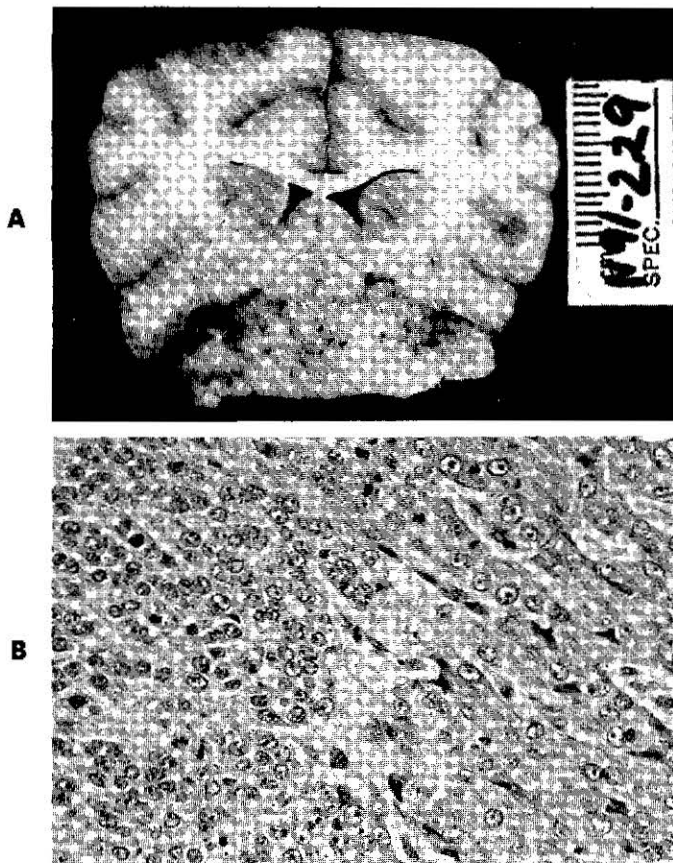


Fig. 6-36. Germ cell tumor, dog. **A**, Large expansile suprasellar mass compresses cerebrum. **B**, Cytology: primitive germ cells (left) and cords resembling hepatocytes. (H&E, $\times 350$.)

locations: in the pineal gland and above or adjacent to the sella turcica. The latter are designated suprasellar, intrasellar, or perichiasmatic, if near the optic chiasm. In humans, most extragonadal germ cell tumors are pineal and occur predominantly in males. In the dog they occur in the suprasellar area, and such germ cell tumors have been designated teratocarcinoma,^{27,28} intracranial germinoma,²⁹ or malignant germ cell tumor.³⁰ These cases present as acute neurological disease in middle-aged **dogs**, often 3 to 5 years of age. The Doberman Pinscher seems to show a predisposition for the development of this tumor. Clinical signs relate to diencephalic compression (lethargy, depression, or stupor) and deficits are referable to multiple cranial nerves, especially the oculomotor, and sometimes the optic chiasm or tract. Pupillary dilation, ptosis, and poor light preservation reflexes are common. At necropsy, a large, grayish white, midline extramedullary mass covers and adheres to the ventral aspect of the diencephalon (Fig. 6-36, A). The pituitary gland is usually obliterated. These tumors may be huge, extending from the olfactory peduncles to the pons and laterally, covering the pyriform lobes. Transverse sec-

tion of the brain reveals dramatic compression of the hypothalamus, thalamus, and, to a variable degree, more lateral structures. Cranial nerves III and IV are commonly trapped within the neoplasm,²⁸ and any from II to VII may be involved. The mass may adhere to the cranium and infiltrate the dura. Microscopically, the neoplasm is divided into lobules separated by collagenous septae. Areas of necrosis and mineralization are observed. The cell type may be predominantly of one type, but the following mixed populations are characteristic (Fig. 6-36, B):

1. Germinomatous areas, comprising moderately pleomorphic cells with round to ovoid nuclei, granular chromatin, and a single nucleolus, and cytoplasm that varies from indistinct to moderately abundant and amphophilic; up to four mitotic figures per high-power field
2. Nests of cells reminiscent of hepatocytes with ovoid vesicular nuclei, a prominent nucleolus, abundant pale amphophilic cytoplasm, and sometimes one or two large, cytoplasmic, lipid-positive vacuoles
3. Acini and tubules of tall columnar epithelial cells with goblet cells and an eosinophilic, PAS-positive secretory substance, areas that may resemble intestinal or respiratory epithelium

Infiltrating these fields of mixed neoplastic cells are lymphocytes that form small accumulations. In a second pattern, the tumor cells are predominantly of the germ cell type with considerable lymphoid influx and many syncytia. One such example³⁰ had disseminated along the cranial leptomeninges. Immunocytochemically, these tumors in humans express α -fetoprotein (AFP), human chorionic gonadotrophin, and placental alkaline phosphatase. We have observed positive staining for AFP in the canine tumor.³⁰

A few mature intracranial teratomas have been described in animals (cow, rabbit) and in the chicken, containing elements of all three germ cell layers.³¹

Craniopharyngioma

Craniopharyngiomas are suprasellar tumors of some importance in childhood. In humans they lie above the sella turcica and by their expansion compress the pituitary gland, optic chiasm, and hypothalamus. Necrosis, calcification, cholesterol deposition, and cystic change are common, with turbid brown contents described as resembling crank case oil. Mineralization may be evident radiographically. Microscopically, in solid areas, cords of epithelium within a fibrous stroma recapitulate the ameloblastoma of the jaw; cystic areas are lined by a flattened epithelium (Fig. 6-37). A few cases have been claimed in the dog, conforming more or less to the human tumor; in some the diagnosis is in doubt. In the dog, polygonal to squamous epithelial components have been described.³² Because of hypophyseal-hypothalamic injury, diabetes insipidus, obesity, and atrophy of the genitals may ensue.³³ Their origin is from remnants of the craniopharyngeal duct ectoderm.



Fig. 6-37. Craniopharyngioma, human. Microcystic pattern. (H&E, $\times 350$.)

Chordomas

Chordomas, rare tumors in animals³⁴ and uncommon in humans, are derived from the intraosseous remnant of the notochord. In humans approximately half are sacrocaudal; they are slow-growing, locally destructive of vertebrae or the cranium, and may extend to adjacent soft tissue, including the spinal cord and brain.³⁵ A few have been observed in the dog,³¹ cat,³⁶ rat,³⁷ mink,³⁴ and ferret.³⁸⁻⁴⁰ Grossly they are firm to cystic, nodular masses with dense, fibrous trabeculae. Microscopically, the characteristic physaliphorous cells have bubbly, vacuolated cytoplasm and a small, dark central or eccentrically placed nucleus (Fig. 6-38). Extracellular pools of mucin are prominent and stain with PAS and mucicarmine preparations. Basioccipital human chordomas show a cartilaginous differentiation, so-called **chondroid chordoma**. This variant has been reported in mink.³⁴ Chordomas contain keratin and vimentin intermediate filaments.³⁹⁻⁴¹

Intradural-extramedullary spinal cord tumors in young dogs

Gliomas of the spinal cord (astrocytoma,⁴² oligodendroglioma) are much less common than their counterparts in the brain. In most studies of dogs and cats with tumors involving the spinal cord, extramedullary tumors far exceed primary neuroectodermal neoplasms. Of major importance are nerve sheath tumors, vertebral osteosarcomas and other sarcomas, lymphomas, meningiomas, and miscellaneous metastatic tumors that have seeded to vertebral bodies or spinal cord parenchyma.⁴³⁻⁴⁶

There is a unique **intradural extramedullary spinal**

cord tumor that occurs in the young **dog**. Our experience at Cornell of 12 cases and 13 others previously published has been reviewed.⁴⁷ Most affected dogs are 5 to 36 months of age, and German Shepherds may have a predisposition to developing this tumor. Males and females are affected equally. Presenting signs are of progressive symmetrical or asymmetrical paraparesis and ataxia. Myelograms demonstrate an intradural enlargement that always occurs between T10 and L2. At autopsy, a tan to gray extramedullary tumor is found within the dura, producing remarkable compression of the spinal cord (Fig. 6-39). One is amazed how well these dogs can still walk. A single mass is found without dissemination along the spinal cord or evidence of neoplasia in other tissues. The histological finding is of admixed tubules and acinar formations blending into solid areas of fusiform cells. Sometimes, structures that could be taken for rudimentary glomeruli can be found (Fig. 6-40). Attempts to demonstrate neuroectodermal antigens in the mass, such as GFAP, neurofilament, and neuron-specific enolase, are unsuccessful,^{47,48} whereas the rosettes may stain for cytokeratin. Ultrastructural findings are of nests of cuboidal to columnar epithelial cells with apical intercellular junctions, surface microvilli and occasionally cilia, and a delineating basal lamina (Fig. 6-41).

This neoplasm has most frequently been reported as an ependymoma despite its extramedullary location. Neuroepithelioma has also been proposed.⁴⁹ The diagnosis of germ cell tumor is perhaps worth pursuing, but this entity differs microscopically from the intracranial germ cell tumor of the dog.³⁰ The suggestion by Bridges, Storts, and Read⁵⁰ that

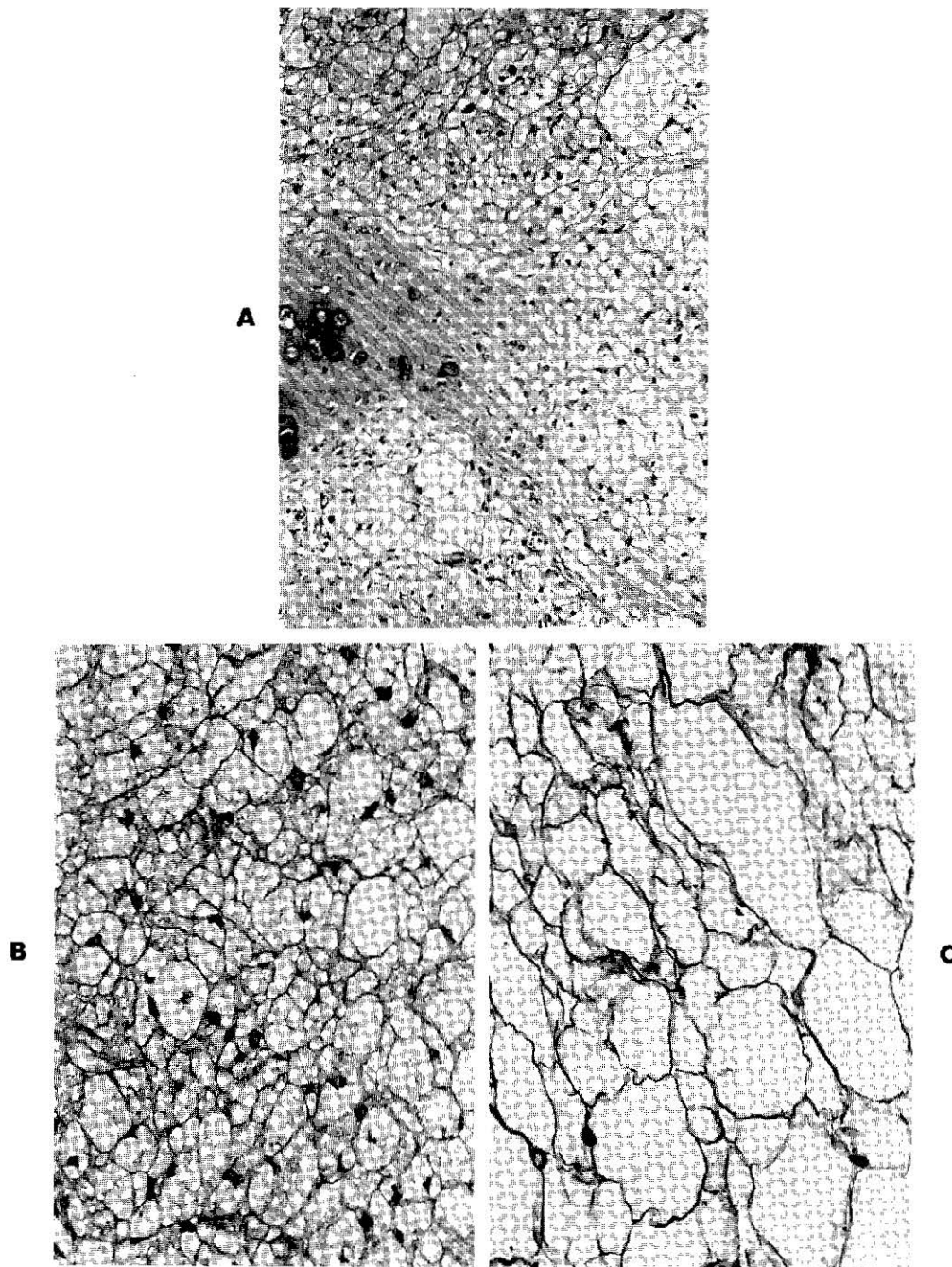


Fig. 6-38. Chordoma, ferret. **A**, Chondroid chordoma. (H&E, $\times 140$.) **b**, Bubbly physaliphorous cells. (H&E, $\times 350$.) **C**, Cytokeratin immunocytochemistry. ($\times 350$.)

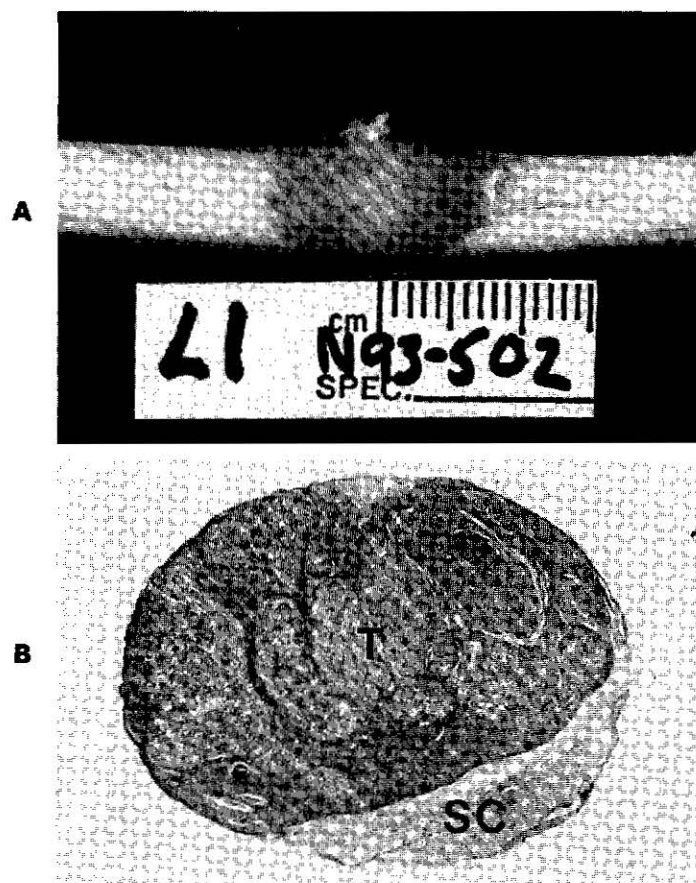


Fig. 6-39. Young dog spinal cord tumor. **A**, Extramedullary mass at L1. Dura has been removed. **B**, Cross section of tumor (*T*) and remnants of spinal cord (*SC*).

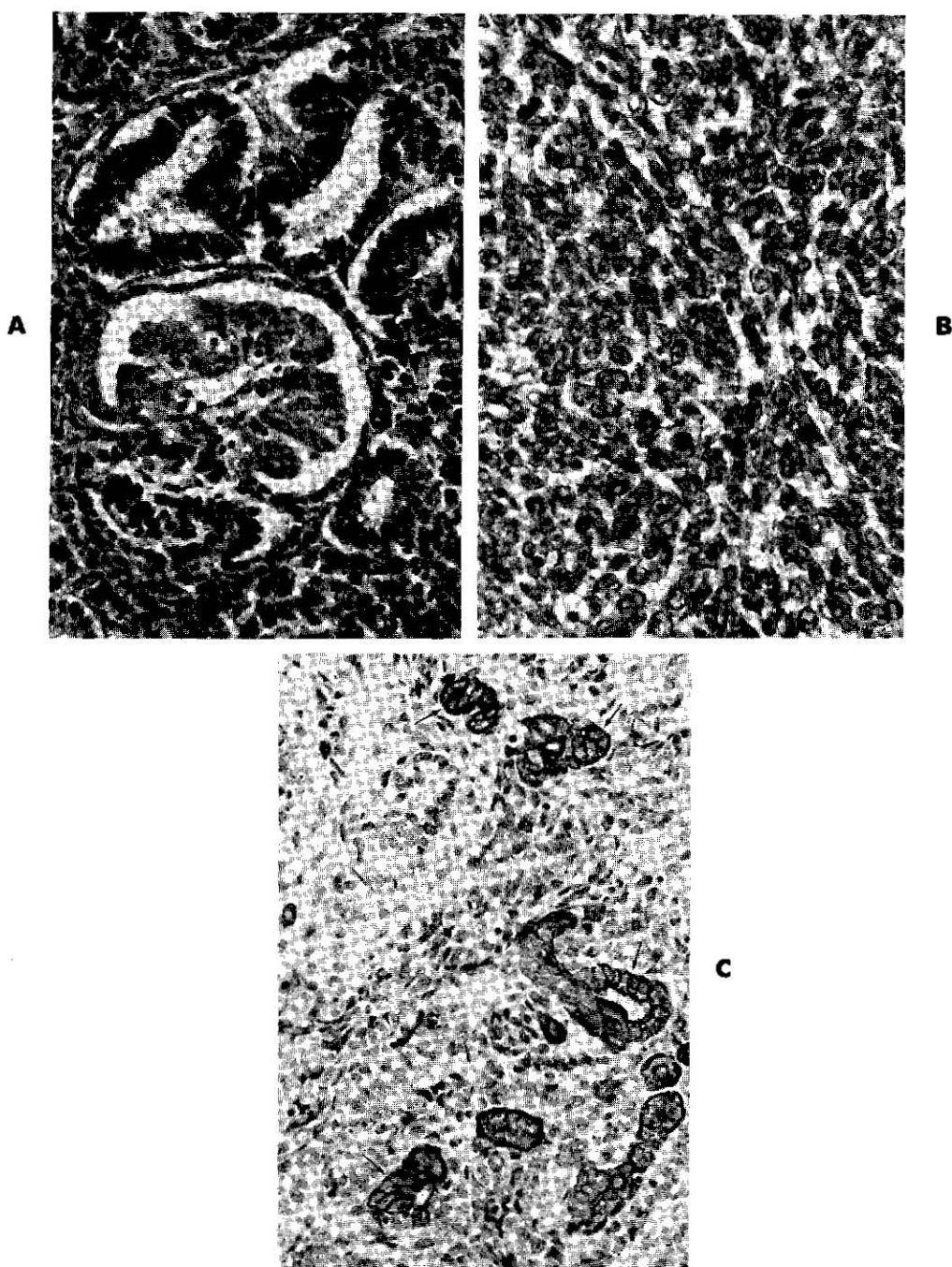


Fig. 6-40. Young dog spinal cord tumor. **A**, Tubules and a primitive glomeruloid structure. (H&E, $\times 350$.) **B**, Area of solid blastema. (H&E, $\times 350$.) **C**, Epithelial elements express cytokeratin (arrows.) (Immunocytochemistry, $\times 350$.)

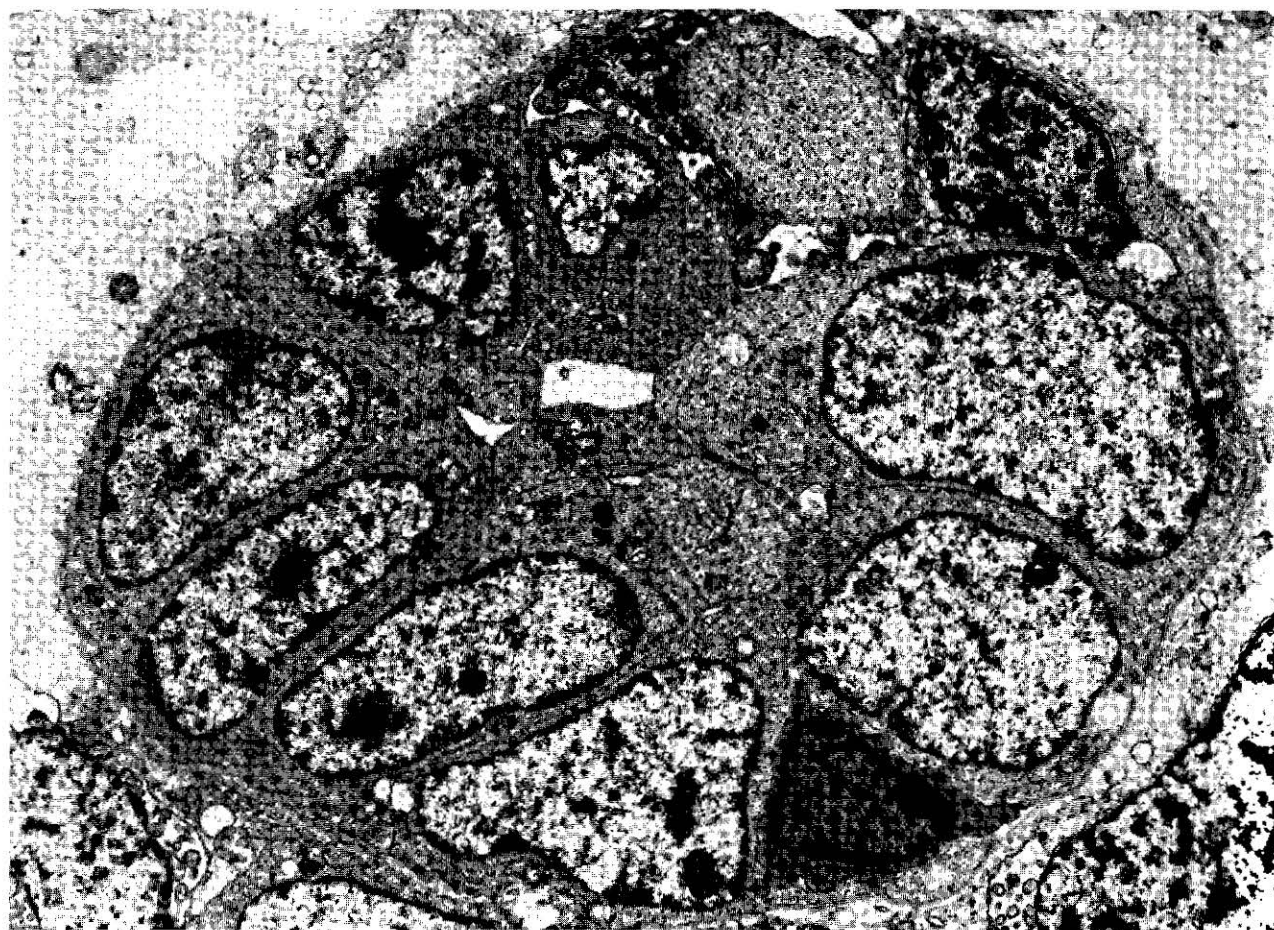


Fig. 6-41. Young dog spinal cord tumor. Ultrastructural features of an epithelial rosette. ($\times 6400$.)

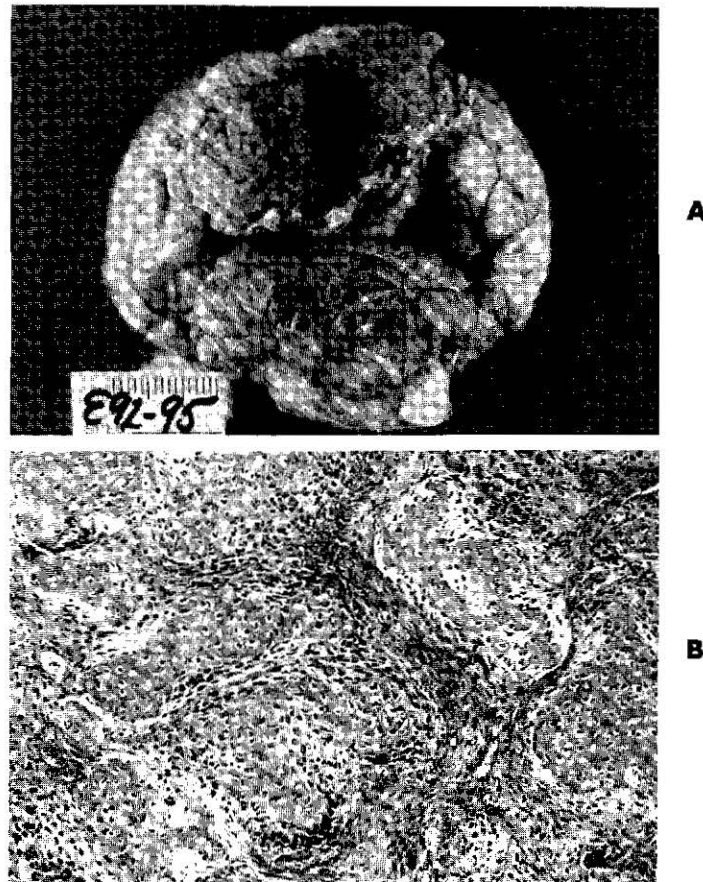


Fig. 6-42. A, Multilobular osteochondroma arising from occipital bone and tentorium, dog. B, Multiple lobules of osseous and chondroid tissue. (Masson's trichrome, $\times 140$.)

this may be a nephroblastoma, presumably primary and ectopic, is intriguing. In collaboration with Dr. J. Roth, we have found that this tumor is recognized by a monoclonal antibody raised to the long-chain form of polysialic acid.⁵¹ This molecule, a component of the neural cell adhesion molecule, is expressed by embryonic kidney cells and human nephroblastoma.^{52,53}

Skeletal tumors

Primary skeletal tumors are a sporadic cause of neurological disease. In the dog, **multilobular osteochondroma** or osteochondrosarcoma occurs with some frequency in the cranium (Fig. 6-42).⁵⁴ Vertebral osteochondromas may be seen in young animals.^{55,56} Multiple osteochondromas are also known as multiple cartilaginous exostoses. Osteosarcomas and chondrosarcomas of the vertebrae are seen in mature and aged dogs.^{44,45}

References are on page 400.

METASTATIC CENTRAL NERVOUS SYSTEM TUMORS

Many primary visceral tumors, particularly carcinomas, have the potential for wide dissemination including spread

to the CNS. Involvement of the neuraxis seems to be less common in animals than in humans. There may be several reasons for this apparent biological difference. In animals with malignant tumors, the option of euthanasia is always available and often is practiced. Accordingly, termination may occur before the neoplasm has shown its full metastatic potential. Further, CNS micrometastases may be present but subclinical at the time of euthanasia; such cases are identified only if the brain is examined postmortem as a matter of course. Anatomical differences in the disposition of the aortic arch, brachiocephalic trunk, and carotid arteries may favor seeding to the brain less in animals than in humans. Finally, relative differences in both tumor incidence and biological behavior may also be of importance. In humans, approximately 40% of lung cancers metastasize to the brain,¹ and some patients present with neurological disease and silent pulmonary tumors. Pulmonary tumors in dogs are much less common than in humans, and reports of CNS involvement are few.^{2,3}

Metastatic disease can involve tumors arising in proximate or distant tissues. **Squamous cell carcinomas** of the paranasal sinuses⁴ or the eye^{5,6} of cattle invade the cranium, sometimes along cranial nerves. In dogs, **nasal carcinomas**

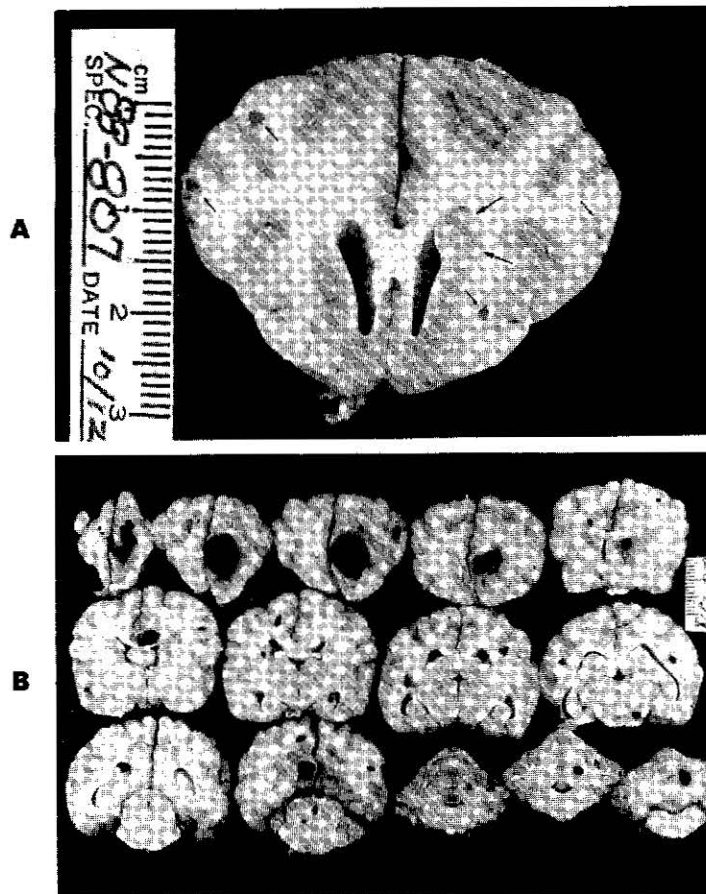


Fig. 6-43. Metastatic brain tumors, dog. **A**, Adenocarcinoma. Some masses are cystic (small arrows), others are solid (large arrows). **B**, Hemangiosarcoma.

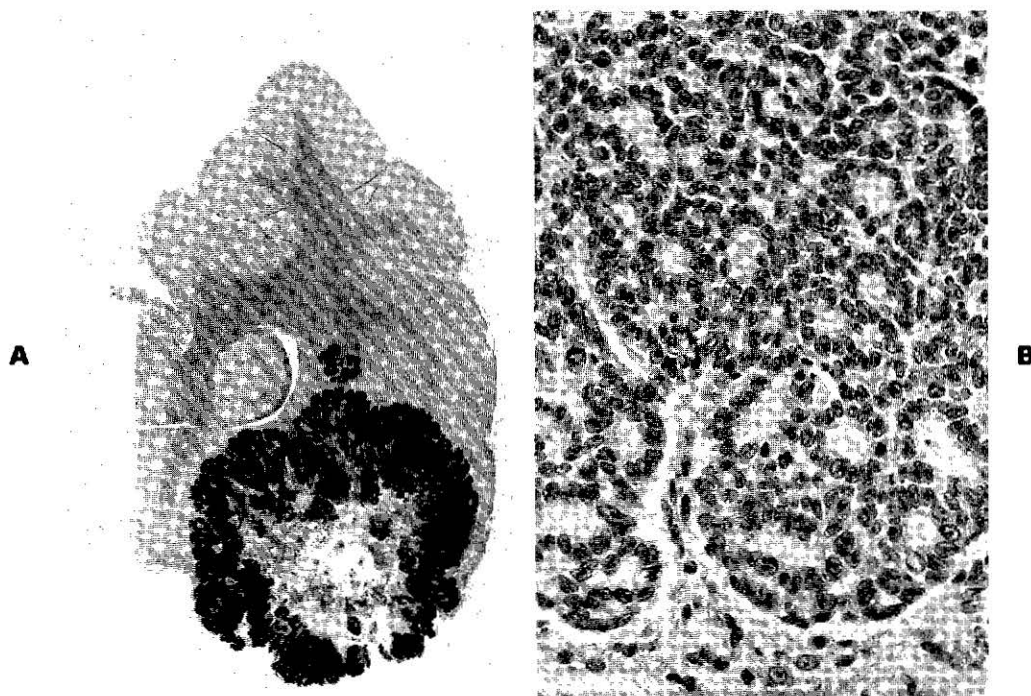


Fig. 6-44. Metastatic mammary adenocarcinoma, cat. **A**, Tumor in temporal lobe. (H&E, $\times 5$.) **B**, Detail of adenocarcinoma. (H&E, $\times 350$.)

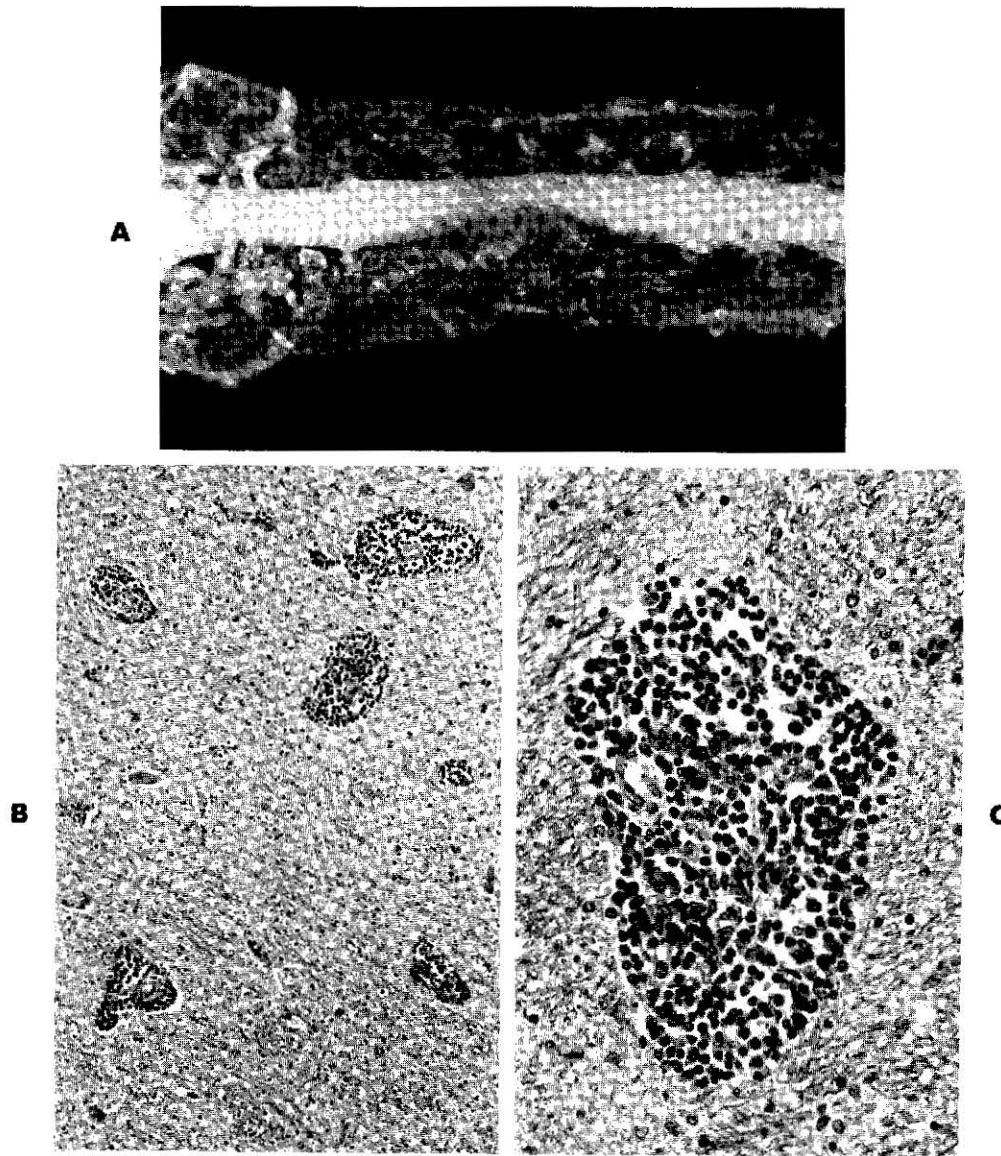


Fig. 6-45. Lymphoma. **A**, Cat. Extradural mass compresses cervical spinal cord **B**, Brain stem, horse. Neoplastic lymphocytes form cuffs about several blood vessels. (H&E, $\times 140$.) **C**, Cell detail in perivascular cuff. (H&E, $\times 350$.)

invade the cribriform plate and infiltrate the olfactory bulb and frontal lobe of the brain.^{7,8} Hematogenous seeding from a distant site is more common. In a series of 400 spontaneous CNS tumors in animals, 17% were metastases.⁹ In humans, studies have shown that certain tumors consistently establish metastases in certain areas of the brain;¹⁰ for example, carcinomas of the breast are most often found in the basal nuclei and cerebellum.¹¹ For animals, only generalizations are possible. Gray matter areas seem to be sites of predilection for seeding, particularly the cerebral cortex,¹² hippocampus, and cerebellar cortex. For some tumors, such as **malignant melanoma** and **hemangiosarcoma**,¹³ the brain is commonly peppered with numerous small masses. In contrast, carcinomas (lung, mammary gland) often produce

fewer, larger secondary tumors (Figs. 6-43 and 6-44). However, these are generalizations, and considerable variation occurs from case to case. Metastatic tumors, unlike many (low-grade) gliomas, are sharply circumscribed, often of distinctly different color from surrounding CNS tissue (perhaps due to hemorrhage), and may "shell out" in the process of brain cutting. Slowly expanding masses in white matter may produce considerable brain edema.

Metastasis may be to the cranium or vertebrae as with **multiple myeloma**¹⁴ and **prostatic carcinoma**. In dogs, **aortic body tumors** and other chemodectomas metastasize to the vertebrae with some frequency.¹⁵⁻¹⁸ As a sequel to vertebral metastasis, spinal cord injury may follow either from local invasion of the epidural space or pathological



Fig. 6-46. Angiotropic lymphoma, dog. Neoplastic cells within meningeal veins, thalamus. (H&E, $\times 350$.)

fracture of bone. The sequence of tumor expansion—from the vertebral body bone marrow, through the cortical foraminae of penetrating veins, and into the vertebral canal—has been studied with experimentally induced vertebral tumors in mice.¹⁹ Blood-borne neoplasms may find hemopoietic bone marrow to be fertile soil because of the growth factors it contains.

Selective seeding to the leptomeninges and choroid plexuses is uncommon in animals. Diffuse meningeal involvement with epithelial tumors is referred to as **meningeal carcinomatosis**, for example, from an intestinal carcinoma.²⁰ Extensive leptomeningeal and choroid plexus infiltration is occasionally seen in dogs with multicentric lymphoma and neoplastic cells may be identified in CSF.²¹ Focal extradural tumors producing spinal cord compression have been observed in gray horses with malignant melanoma.²²

Lymphomas are one of the more important non-neuroectodermal tumors of the CNS and deserve brief comment. In **cats**²³⁻²⁵ and **cattle**,²⁶ CNS lymphoma is seen with some frequency as part of multicentric disease and occasionally as the only lesion.^{27,28} Most commonly, lymphoma occurs as an epidural mass in the vertebral canal (Fig. 6-45, A). Intracranial lymphoma usually involves the leptomeninges or the choroid plexus. Leptomeningeal spinal cord involvement is least common. Clinical signs relate to progressive compression of the nervous system at the site of the mass. Myelography is of assistance in demonstrating the site of a tumor in the vertebral canal and that it is extradural. At necropsy, these are usually soft, dull white nodular

masses within the vertebral canal that can readily be mistaken for epidural fat. Less commonly, the tumor is intradural (leptomeningeal) and may infiltrate spinal nerve roots. Microscopically, these tumors are identical to lymphomas of other organs. CNS lymphoma is less common in the **horse**, has been reported in the epidural space with spinal cord compression,²⁹⁻³² and can involve the parenchyma (Fig. 6-45, B and C).

In **dogs** most cases of CNS lymphoma are manifestations of multicentric disease.^{21,33} The syndrome of neoplastic angioendotheliomatosis has been reported in dogs^{34,35} and is now thought to be an **angiotropic lymphoma**³⁶ (Fig. 6-46), which often involves the CNS in humans. The tumor is characterized by a largely intravascular pattern of growth of neoplastic cells. Neurological manifestations of extraneural lymphoma are described in the dog and cat and may be manifestations of hyperviscosity^{37,38} or other paraneoplastic effects.

Involvement of the CNS (or the PNS) in leukemia is rare in animals; it has been recorded in myelomonocytic leukemia in the dog.³⁹

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Chapter 7 DISEASES OF THE PERIPHERAL NERVOUS SYSTEM

Introduction and general pathology of the peripheral nervous system

INTRODUCTION

The **peripheral nervous system** (PNS) consists of cranial as well as spinal nerve components. It includes the dorsal and ventral roots, spinal ganglia, spinal and specific peripheral nerves, cranial nerves and their sensory ganglia, and the peripheral components of the autonomic nervous system (i.e., preganglionic and postganglionic fibers and the autonomic ganglia). Most of these components of the PNS are located in part within the CNS. The somatic motor fibers of the ventral roots originate from cell bodies in the spinal ventral horns; autonomic fibers arise from preganglionic cell bodies in the zona intermedia at thoracolumbar and sacral spinal levels and in cranial nerve nuclei in the brain stem; primary sensory neurons with cell bodies in spinal and cranial nerve ganglia have central projections and terminations.

The functional or impulse-conducting components of the peripheral nerves are the axons or nerve fibers. Most axons exceeding 2 μm in diameter are insulated by a segmentally applied, lamellated myelin sheath. Many axons less than 2 μm in diameter are unmyelinated. The mean diameter for unmyelinated axons in most species is about 1 μm ,¹ but the range, for example, in the horse, is from 0.5 to 2 μm .²

The nerve fibers—that is, axons and their sheaths—in mixed peripheral nerves have been separated into A, B, and C groups on the basis of their conduction velocity as recorded in a compound action potential.^{3,4} The correlation between conduction velocity and nerve fiber diameter provides a basis for morphological separation as well. Fibers in the A group are myelinated and range from 2 to 20 μm in diameter. They can be subdivided into α and δ categories. The A α fibers are the largest and conduct at 30 to 120 m/

second. They include the somatic motor fibers and large proprioceptive afferent fibers. The A δ fibers are smaller, at 2 to 5 μm in diameter, and they convey nociceptive and other afferent impulses at a velocity of 5 to 30 m/second. The B fibers are myelinated, preganglionic, autonomic fibers that measure 1 to 3 μm in diameter and conduct at 3 to 14 m/second. The C fibers are unmyelinated. They measure from 0.1 to 1 μm in diameter and conduct at a velocity of 2 m/second or less. The C fibers include autonomic postganglionic fibers and afferent fibers conveying thermoeceptive and nociceptive impulses.

Axons are delimited by an 8-nm-thick plasma membrane, the **axolemma**. Within the axolemma, the axonal cytoplasm or **axoplasm** appears as a clear matrix containing various organelles, including microtubules, neurofilaments, mitochondria, and smooth endoplasmic reticulum.

With standard histological fixation and processing, the neurofilaments and, to some extent, the microtubules in aggregate form the **neurofibrils** that are impregnated on silver preparations. Such silver reduction methods, by densely impregnating these cytoskeletal organelles, stain the axon and allow microscopic assessment of its continuity and dimensions. The **microtubules**, composed of tubulin protein dimers, are hollow-core cylinders that measure 25 nm in diameter. They course longitudinally but as individuals fail to extend over the full length of the axon. Axonal microtubules are postulated to be relatively short, occurring at lengths of 10 to 20 μm .⁵

Microtubules play an essential role in axon transport. Axons lack the ribosomal aggregates that form the Nissl substance found in the perikaryon and dendrites. Without ribosomes the axon is incapable of in situ protein synthesis.

The maintenance and renewal of the axon and its endings, therefore, are dependent upon the transport of vital materials from the cell body. Rapid anterograde transport, which proceeds at rates up to 400 mm/day, provides for the structural and metabolic needs of the axon terminals.⁶ In this transport, the microtubules appear to serve as rails, and **kinesin**, a myosin-like protein, furnishes the motive force necessary to deliver vesicles and materials for renewal to the synaptic regions of the axon.^{7,8} Slow axonal transport, which progresses in anterograde fashion in two rate groups of 1 and 2 to 4 mm/day,⁹ provides for the maintenance of the structural integrity of the axon. Microtubule and neurofilament components progress down the peripheral axons at the slow component a (SCa) rate of about 1 mm/day. **Dynamin**, a microtubule-associated motor protein, has been suggested as the mechanochemical enzyme that mediates slow transport of microtubules.⁵ The SCb rate group of transported proteins are diverse and include actin and clathrin along with many others.

Neurofilaments are a type of intermediate filament found in all mammalian neurons. They measure about 10 nm in diameter. Neurofilaments are composed of three peptide subunits with molecular weights of 68,000 (NF-L), 150,000 (NF-M), and 200,000 (NF-H). The NF-L forms the filament core, and the NF-M and NF-H are arranged around this axis. The macromolecular form in which the neurofilaments undergo anterograde transport and the proportion of filaments undergoing simultaneous transport are currently under investigation. There is some evidence from transected nerve experiments that neurofilaments can be transported bidirectionally.¹⁰ Neurofilaments are crucial cytoskeletal elements that stabilize the axon and ensure its radial growth.^{11,12} Pathological conditions that affect the anterograde transport of neurofilaments have been thought to alter axon diameter, leading to regional swelling or atrophy (Fig. 7-1).¹³ The phosphorylation of neurofilament protein subunits at their amino-terminal head domains and carboxy-terminal tails by protein kinases is crucial to normal maintenance of the neuronal cytoskeleton. It is suspected that changes in the timing of phosphate addition and turnover at specific sites on the subunits as neurofilaments move into and down the axon may explain neurofibrillary lesions that occur in the cell bodies or axons in certain diseases.¹⁴

Recently, a second neuron-specific intermediate protein has been identified. This protein, called **peripherin**, has an apparent molecular weight of 58,000. Peripherin is located mainly but not exclusively in neurons with relatively long axons that, at least in part, extend into the PNS, such as α -motor, spinal ganglionic, sympathetic, and parasympathetic neurons.^{15,16} The function of peripherin filaments in the neuron is unknown at present.

Retrograde transport in the axon progresses at a rate approximately half that of rapid anterograde transport, that is, 200 mm/day. This transport also is dependent on microtubules. The microtubule-associated protein 1C, a cyto-

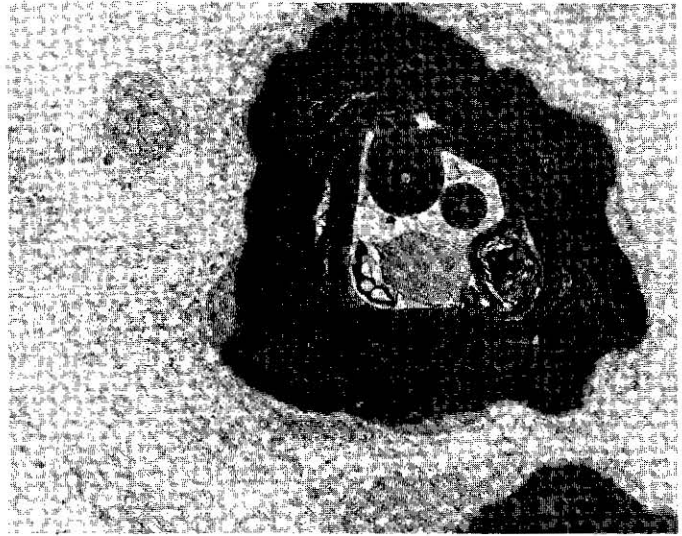


Fig. 7-1. Axonal atrophy. Equine motor neuron disease, lumbar spinal root. ($\times 8750$.)

plasmic form of the flagellar ATPase, **dynein**, produces the motive force for retrograde translocation.^{17,18} It is through retrograde transport that effete organelles and membranes are cleared from the terminal axon and conveyed back to the cell body for degradation by perikaryal lysosomes. Retrograde transport also conveys neurotrophic substances (retrophins), which are taken up by endocytosis at the axon terminals and conveyed to the cell body, where they maintain neuronal viability.¹⁹ The first identified and best known of these is **nerve growth factor**, which is essential for the normal development of sympathetic and sensory neurons.²⁰

Ciliary neurotrophic factor (CNTF), a 20,400-KD protein,²¹ was initially recognized for its *in vitro* effects on the parasympathetic neurons of the ciliary ganglion.²² It has been shown to support the survival of facial motor neurons that would typically succumb to early postnatal axotomy.²³ It may be that this retrophin is produced by ensheathing Schwann cells as well as terminal target cells.²⁴ Retrograde transport also has been implicated in conveying the signal for the axon reaction. Thus, central chromatolysis and the regenerative surge in protein synthesis that follows axon interruption are initiated by a signal that is conveyed back over the surviving length of axon to the cell body. Retrograde transport also can inflict extreme damage when it delivers neurotrophic viruses (e.g., rabies, pseudorabies), or toxins (e.g., tetanus) from the periphery.^{25,26}

Besides cytoskeletal components, axons contain membranous organelles including mitochondria and smooth endoplasmic reticulum (sER). Mitochondria are usually disposed longitudinally and sometimes are closely related to microtubules. Mitochondria undergo slow anterograde transport, and their localized accumulation along with other membranous bodies within swollen axons is often associated

with a disturbance in axon transport. Profiles of sER within the axon appear as vesicles. These profiles are clearly larger than the microtubules and filaments with which they are interspersed.

Schwann cells invest both myelinated and unmyelinated axons in the peripheral nervous system.¹ The insulating sheath of **myelin** consists of 75% lipid and 25% protein. The lipids include phospholipids, glycolipids, and cholesterol. Most of the protein, approximately 60%, is glycoprotein, and the predominant glycoprotein is the P_0 . The P_1 and P_2 basic myelin proteins make up another 10% to 20%, and the recently described peripheral myelin protein 22 accounts for 5%.^{27,28} Ultrastructurally, the mature myelin sheath is seen on transverse sections as a series of compact, 12-nm-wide lamellae applied as a concentric wrap by Schwann cells. Over the length of an axon, the myelin sheath is applied segmentally as a series of internodes. The myelin of the internode is a very extensive, spiraled, and compacted sheet of Schwann cell plasmalemma. Recent work suggests that the concentric wrap is applied by progressive spiraling of the leading edge or tip of the adaxonal lamella.²⁹ One internode is the length of myelin applied by a single Schwann cell. The nodes of Ranvier, which appear as narrow interruptions in the myelin sheath, mark the gaps between adjoining Schwann cells. Series of internodes can be demonstrated well on single axons that have been teased out of osmicated peripheral nerve fascicles and mounted individually for microscopic examination. The length of an internode varies with the diameter or perimeter of the axon. Similarly, the thickness of the myelin sheath varies directly with the axon perimeter. Thus, the axons with the greatest perimeter generally have the longest internodes (i.e., greater than 1 mm) and the thickest myelin. Yet, the myelin thickness to axon perimeter relationship may vary significantly between peripheral nerves.³⁰ Moreover, the myelin-axon relationship may differ between levels of the same nerve and also at corresponding levels of the same nerve on the left and right.³¹

The proportional relationship between axon and myelin can be greatly modified by peripheral nerve diseases. For example, many conditions that bring about segmental loss of myelin result in a proliferation of Schwann cells. These cells, then in excess, capture places along the denuded length of axon and restore the myelin sheath. The restored or intercalated internodes, however, differ from the original intact internodes that precede and follow them along the axon in that they are notably shorter and their myelin thickness is reduced. Similarly, the internodes formed along regenerated axons are also thinner and shorter than the originals. It has been demonstrated in normal, remyelinated, and regenerated nerve fibers that there is a close correlation between the volume of myelin in an internode and the surface area of the axolemma beneath the internodal sheath.³² In conditions that cause axon atrophy, the myelin sheaths appear greatly and disproportionally thickened around the

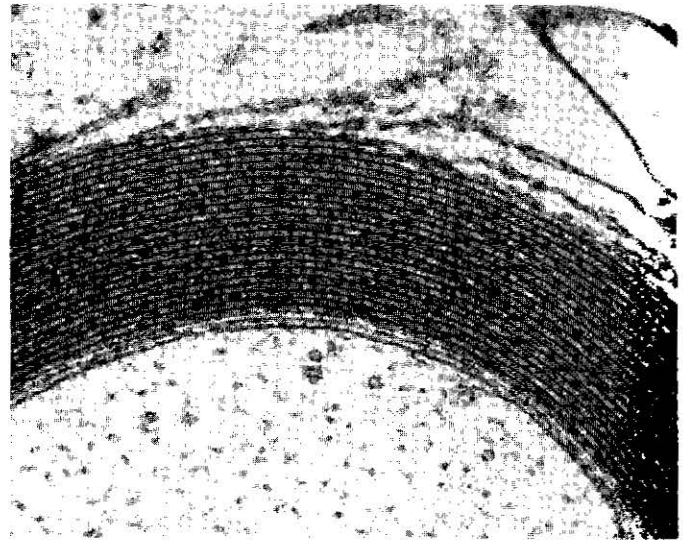


Fig. 7-2. Normal canine myelinated axon, which contains neurofilaments and microtubules. In the myelin sheath, the major dense line is prominent. ($\times 87,500$.)

shrunken axon,³³ yet quantitative studies reveal that myelin thickness remains unchanged during reduction of the axon diameter.³⁴

In mature myelin, each compact lamella or Schwann cell layer contains a central, **major dense line** (Fig. 7-2). This line, measuring about 3.5 nm wide, marks the inner or cytoplasmic aspects of the plasma membranes, which are closely apposed because the intervening cytoplasm has been eliminated. The external faces of the membranes of adjoining lamellae are opposed to form a less dense, but bisected, 5.5-nm **intraparallel line**.³⁵ The basic repeating unit in peripheral myelin (i.e., the distance between adjacent dense lines) is greater in peripheral than in central myelin. This periodicity on routine ultrastructural preparations measures 12 nm in peripheral myelin versus 10.6 nm in central myelin.³⁶ On freeze-etch preparations, a peripheral period of 18.5 nm contrasts with a central myelin repeat of 16 nm.³⁷ This difference is attributable in large measure to the greater splitting at the intraperiod line in peripheral myelin. The P_0 myelin protein in part is situated in the intraperiod line, where it is thought to help in stabilizing the myelin sheath. The basic myelin proteins are thought to have a major part in compacting the myelin lamellae at the major dense line.²⁷

Microscopic study along an internode reveals multiple funnel- or chevron-shaped interruptions in the staining of the myelin sheath. These are called **Schmidt-Lantermann clefts** or incisures, and ultrastructurally each appears as a staggered series of openings of the major dense lines. In these openings there are small residual pockets of Schwann cell cytoplasm. It has been suggested that in aggregate they may impart some resiliency to the sheath, so that with increasing tension they would permit slight elongation of the

internodes. Various functions have been attributed to the incisures. The incisures also would appear to establish a continuous helical path for metabolites through the myelin sheath. This route might allow for turnover of myelin membrane components and provide access for metabolites to the periaxonal space.³⁸

The periaxonal space that intervenes between the innermost membrane of the Schwann cell and the axolemma communicates with the extracellular space at the node of Ranvier. This 20-nm periaxonal space is maintained by a 100-KD, intrinsic, **myelin-associated glycoprotein (MAG)**, whose heavily glycosylated portions project from the periaxonal Schwann cell membrane. In the quaking mouse mutant, MAG is not expressed, and its lack results in the lack of a periaxonal space.³⁹

There is evidence from freeze-fracture studies that sodium channels are concentrated in the nodal axolemma, the site of action potential generation in saltatory conduction.⁴⁰ At the node, the diameter of the axon is reduced, and the density of microtubules in the axoplasm is increased, along with the concentration of mitochondria and smooth endoplasmic reticulum. On longitudinal section, to either side of the node (i.e., in the paranodal region), the lamellae of the adjoining internodes appear to end as a series of expanded **terminal loops**. In the terminal loops, the major dense lines open as in the incisures and are replaced by cytoplasm. Also as in the incisures, a cytoplasmic continuum progresses helically from the most superficial loop next to the node to the loop of the innermost lamella, which is farthest from the node. The terminal loops of thinner myelin sheaths abut the axon and are adherent to the axolemma. In this paranodal region, the adjoining terminal loops may be attached by desmosomes. The Schwann cell cytoplasmic compartment external to the most superficial myelin lamella is prolonged laterally beyond the last terminal loop into the nodal region. These mitochondria-rich cytoplasmic collars of the adjoining Schwann cells extend over the node and terminate in microvillous processes that extend through an amorphous polyanionic gap matrix to the nodal axolemma.⁴¹ At the EM level, transverse sections through the nodal region present a characteristic but unusual appearance with densely arranged neurotubules and filaments in an axon that is partially or completely surrounded by the microvillous processes from the Schwann cell collars. Additionally, the nodal axolemma is characterized by an electron-dense undercoating. Transverse sections through the paranodal region also are easily distinguished, as the myelin presents a crenated outline, and superficial accumulations of Schwann cell cytoplasm contain large numbers of mitochondria.

The cytoplasm-rich portions of the myelinating Schwann cell include the adaxonal loop that forms the **inner mesaxon** and the external or abaxonal layer. The latter is also a loop, and its plasmalemmal edges form the **outer mesaxon**. The external cytoplasm is prominent at mid-internode, where it contains the elongate nucleus, and toward the node, where

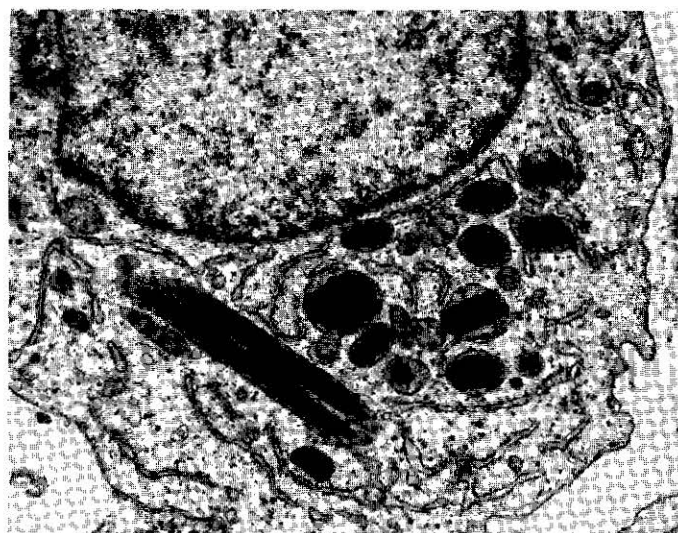


Fig. 7-3. Mitochondrial crystalline inclusions in a macrophage. Neuritis of the cauda equina, horse. ($\times 13,000$.)

it forms the collar and the terminal microvillous processes. The perinuclear cytoplasm is rich in organelles and inclusions. In this perikaryal region, in addition to Golgi membranes, granular endoplasmic reticulum, mitochondria, and dense bodies, one may encounter peculiar elongate, membrane-bound, osmiophilic structures. These, the so-called **pi granules** of Reich, measure approximately 1 to 4 μm in length and contain lamellated interiors. Pi granules are found in the Schwann cells of normal nerves, and they increase with age. They appear to be especially abundant in the Schwann cells of horses.⁴² It is suggested that they, like lipofuscin granules, are residues of lysosome activity.⁴³ Lipid droplets, or Elzholz bodies, as they are sometimes called,⁴⁴ are commonly present in the external layer of Schwann cells in older horses. While these droplets are found in the perinuclear cytoplasm, they also appear at other points along the internode and on teased preparations are seen as small osmiophilic globules adjacent to the myelin sheath. Larger osmiophilic spherical bodies have been observed in the Schwann cell cytoplasm along the internodes of normal goat nerves. These appear to be detached from the myelin sheath and have been called Schwann cell myelin bodies.⁴⁵

On occasion, elongate, osmiophilic, **crystalline inclusions** have also been identified in equine Schwann cells. In addition to Schwann cells, these inclusions have been identified in endoneurial fibroblasts, perineurial cells, and macrophages (Fig. 7-3).⁴⁶⁻⁴⁸ These rodlike inclusions, which appear polygonal or trapezoidal on cross-section, are enclosed in a double membrane. The presence of cristae-like invaginations of the inner membrane indicates that these lamellated inclusions form within mitochondria. Whereas these inclusions have been reported in association with pe-

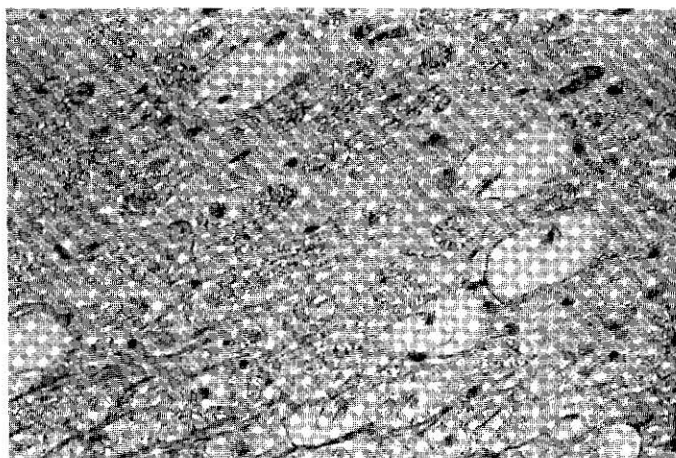


Fig. 7-4. Aging change in myelin. Ballooned myelin sheaths in spinal root, cheetah. (H&E, $\times 350$.)

ipheral nerve disease (e.g., neuritis of the cauda equina) and lymphosarcoma, they have also been found infrequently within Schwann cells of horses without neurological disease. Other than the presence of lipid indicated by strong osmophilia, little is known about the origin of these very unusual mitochondrial inclusions. They may be unique to the horse but are not limited to cells in the peripheral nerves, as they have been encountered in histiocytic cells within equine lymphosarcomas^{49,50} and ciliary epithelium in recurrent uveitis.⁵¹

A change associated with aging that may have functional effects occurs in the myelin rather than the Schwann cell per se. The change, which consists of a focal separation and distension along the myelin internode, is referred to as **myelin blebbing, ballooning, or bubbling** (Fig. 7-4).^{52,54} Myelin bubbles have been identified as an **aging change** in a wide range of mammals,^{55,56} and they are encountered more frequently in the ventral than the dorsal spinal roots.^{53,54} In the rat, the lumbosacral roots are more prominently affected than the thoracic or cervical roots.⁵⁷ Myelin bubbles also occur in the peripheral nerves. Their appearance may portend the development of segmental demyelination. It has been suggested that myelin bubbles and subsequent segmental demyelination develop as a consequence of axon atrophy, an even more drastic change associated with aging.⁵⁸ A senile regression of the neuron is manifest as reduction of cell volume, which includes atrophy of the axon with distal degeneration and consequent skeletal muscle atrophy.⁵⁷ Despite an apparent relation between the two aging phenomena, an experimental study found no association between neurectomy-induced axon atrophy in rats and myelin ballooning in the roots.⁵³

It is possible that dense myelin ballooning in the spinal roots and peripheral nerves may sometimes occur in young animals as a component of neurological disease. For example, myelin ballooning was substantial in young Jack

Russell Terriers afflicted with progressive ataxia⁵⁹ and long-tract degeneration in the spinal cord.

Morphometric analysis of peripheral nerves has revealed that significant demyelination and loss of larger axons occur in aged animals. Teased-nerve studies in the horse suggest a relatively early appearance of age-related changes in the myelin sheath because animals 5 years and older had a mean of 9.6% of nerve fibers with myelin sheath abnormalities.⁶⁰ In the horse, reductions in sensory nerve conduction velocities in older individuals have been correlated with age-related loss of larger myelinated axons.^{61,62} Quantitative histological and teased-fiber studies of peripheral nerves from normal dogs of widely varying ages have demonstrated an increased incidence of degeneration and segmental demyelination and remyelination of larger axons in dogs 10 years of age and older.^{63,64} Similarly, myelin ballooning and segmental demyelination have been identified as age-associated in the cat.⁶⁵ It is well to be aware of these subclinical changes in evaluating biopsy or necropsy samples of peripheral nerves from older individuals.

Unmyelinated axons are also ensheathed by Schwann cells. In performing this function, they are sometimes called **Remak cells**. Many of the smaller unmyelinated axons are near the limit of light-microscopic resolution ($0.2\ \mu\text{m}$) so that their relation to the Schwann cells can be discerned clearly only with the electron microscope. Ultrastructural studies reveal that unmyelinated axons are ensheathed by Schwann cells that are arranged in elongate cords and that these cords undergo repeated branching and anastomosis. At the light-microscopic level, these cords have a very cellular appearance on longitudinal section and may be confused with the cords of proliferated Schwann cells that form in the wake of myelinated axon degeneration, that is, B ngner's bands. At the fine structural level, however, transverse sections reveal the presence of axons in grooves or recessed channels in the Schwann cells. A single transected Schwann cell usually accommodates multiple unmyelinated axons, up to 15 in the horse.² Those axons that are recessed deeply have a mesaxonal invagination of Schwann cell plasmalemma that can be traced to the cell surface. At the endoneurial surface, the plasmalemma of the Schwann cell is completely surrounded by a distinct basal lamina. This basal lamina is typical of all Schwann cells—those associated with myelinated or unmyelinated axons as well as those that are devoid of axons as a result of pathological processes. The basal lamina, like those in other organs, is composed of type IV collagen, laminin, fibronectin, and entactin. Although the Schwann cells of unmyelinated fibers resemble those of myelinated axons, the cytoplasm of the former has a reduced area occupied by mitochondria, Golgi apparatus, and endoplasmic reticulum, but greater density of intermediate filaments.⁶⁶ Some studies have found that the Schwann cell intermediate filaments consist exclusively of vimentin, but glial filament protein immunostaining has been reported in sites where unmyelinated axons predominate.⁶⁷

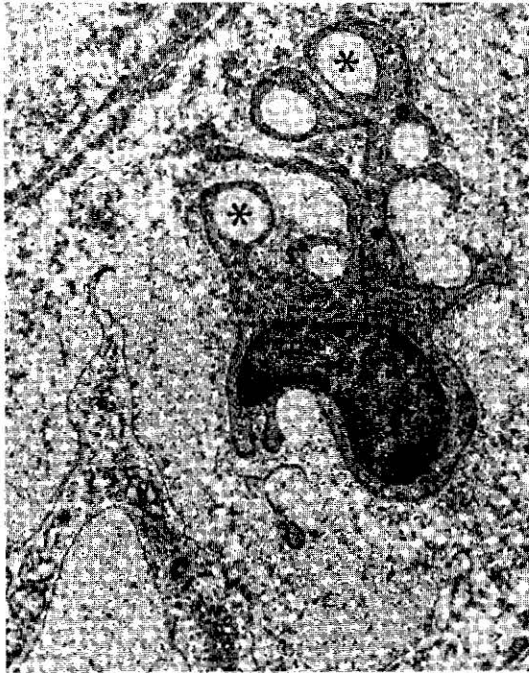


Fig. 7-5. Collagen pockets (asterisks) formed by processes of a Schwann cell. Equine peripheral nerve. ($\times 9100$.)

In the Remak or Schwann cells, some of the grooves that usually contain unmyelinated axons may, on occasion, instead contain small longitudinal bundles of collagenous fibrils. These are called **collagen pockets**.^{68,69} In some Schwann cell profiles, collagen pockets occur in addition to unmyelinated axons, but in others the collagen pockets occur exclusively (Fig. 7-5). These occur in peripheral nerves and less often in the spinal roots of normal animals. Their appearance suggests that the Schwann cell may synthesize or engulf collagen to stabilize its position.⁶⁹ Collagen pockets are found with increased frequency in older individuals and in neuropathies in which there is substantial loss of unmyelinated axons.⁷⁰ In these neuropathies, the observed increase in collagen pockets is accompanied by an increase in empty Schwann cell units, that is, Schwann units devoid of axons.⁷¹ These consist of flattened Schwann cell processes that often present spidery profiles on transverse section.^{72,73}

Occasionally in equine nerves, the Schwann cells ensheathing unmyelinated axons have been found to contain inclusions within the endoplasmic reticulum. The inclusions consist of electron-dense, finely granular material that distends the cisternae. The ultrastructural appearance and location of this material are reminiscent of Russell bodies that form in aged plasma cells. The nature and significance of these proteinaceous inclusions in Schwann cells are unknown.

In the peripheral nerves, the myelinated and unmyelinated axons are gathered in bundles or fascicles. Within a

peripheral nerve trunk, multiple fascicles are bound within a loose connective tissue sheath, the **epineurium**. Proximally the epineurium is continuous with the dura mater.⁷⁴ The epineurial connective tissue consists of loose, irregularly arranged, collagenous fiber bundles, fibrocytes, scattered mast cells, and unilocular fat cells. This epineurial fat may be sufficiently abundant to serve as a shock absorber, possibly preventing nerve damage by concussion or compression.

Some studies had suggested that as peripheral nerves progress distally there is considerable intermingling or diffusion of nerve fibers among fascicles. In the dog, however, this may not be the case. Studies based on transection of the L6, L7, and S1 spinal nerves and the subsequent patterns of degeneration in the sciatic nerve and its branches reveal that fibers from a given segment (i.e., a spinal nerve) remain rather well segregated in longitudinal bundles within the parent nerve and its branches.⁷⁵ Similar segregation may also exist in the nerves of the forelimb of the dog as well. For example, transection of the T1 spinal nerve in a dog led to total fiber loss within the caudal cutaneous antebrachial nerve (Cummings, unpublished observation, 1974). This finding suggests that it is highly unlikely that there is extensive intermingling of fibers of different root origins within the ulnar nerve. On examining a transected peripheral nerve trunk, the fascicles that occupy a peripheral position are composed mostly or entirely of fibers that will next leave the parent to form a terminal branch.

When peripheral nerves have not been fixed under tension and are sectioned longitudinally, the fascicles usually contain axons that in register pursue a zigzag or wavy course. Although this is often regarded as a preparative artifact,⁷⁶ it is also perceived as an *in vivo* adaptation that allows peripheral nerves to accommodate moderate stretching without damage.⁷⁷ It is the zigzag course of the axons that, through an optical effect, creates the macroscopic spiral appearance along nerve trunks known as the spiral bands of Fontana. These spiral bands are visible on unfixed, unstained nerves with the naked eye.⁷⁸ When the nerve is tensed, the axons straighten, and concurrently, the spiral bands disappear.

The individual nerve fascicles are delimited by a discrete and highly organized sheath, the **perineurium**.⁷⁹ The thickness of this sheath varies with the diameter of the nerve fascicle. Proximally, where the spinal roots leave the subarachnoid space, the perineurium of nerve splits; the outer part passes between the dura and arachnoid, and the inner part of the perineurium continues on the nerve roots as the inner portion of the root sheath.⁷⁴ Distally, the perineurium branches with the fascicles and becomes progressively thinner. It terminates in an open end just before the termination of the nerve.⁸⁰ The perineurium consists of circularly disposed lamellae composed of flattened cells. The cellular lamellae or sleeves alternate with layers of dense, irregularly arranged collagenous fibrils (Fig. 7-6, A). Most of the

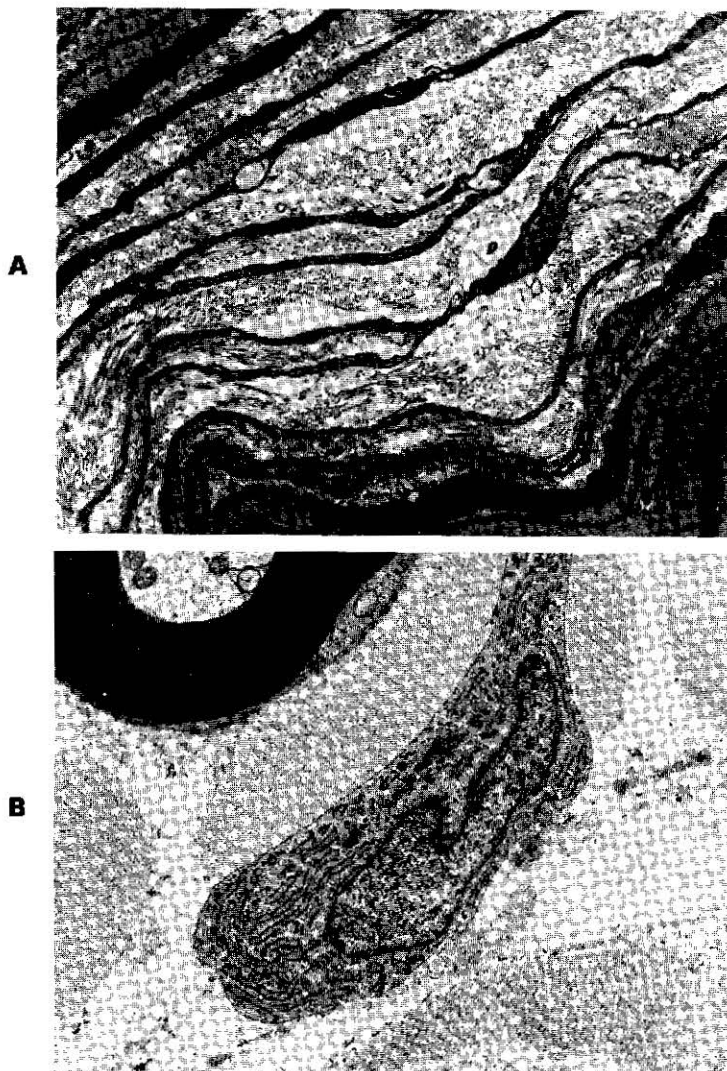


Fig. 7-6. Normal peripheral nerve. A, Perineurium, dog. Slender cell processes alternate with aggregates of collagen fibrils. ($\times 5850$.) B, Endoneurial fibroblast, dog. ($\times 13,000$.)

closely packed fibrils are arranged longitudinally, but some course circularly or obliquely. Each of the cellular lamellae is invested by a complete basal lamina.

The origin of the perineurial cell has been a subject of considerable debate. Its appearance and basal lamina suggested it might be a Schwann cell variant, but immunocytochemical studies have detected differences between these two cell types.⁸¹ Whereas perineurial cells (in contrast to Schwann cells) react with monoclonal antibody against epithelial membrane antigen in humans, they are not labeled with antibodies against S-100 and Leu 7, both of which are expressed by Schwann cells. Recent work indicates that perineurial cells are not of Schwannian origin but are derived from fibroblasts; their abundance of cytoplasmic contractile filaments is like that seen in the myofibroblasts in wound repair.⁸² Within the lamellae, the cells are attached by tight junctions. These perineurial cells have an unusual abun-

dance of caveolae and pinocytotic vesicles, but studies with horseradish peroxidase and other markers reveal little transcytotic movement of macromolecules through the perineurium. Such protein marker studies, instead, suggest that the perineurium serves as a diffusion barrier that, together with the blood-nerve barrier, regulates and protects the intrafascicular environment.⁸³ Moreover, much of the elastic resistance of peripheral nerves to stretching appears to reside in the perineurium.⁸⁴

The **endoneurium** comprises the interstitial connective tissue within the fascicle. The terms endoneurial contents and endoneurial components are applied to all tissues within the perineurium, including the nerve fibers and vessels. The endoneurial collagen is sparse in the roots, but in the nerves it consists of more substantial numbers of longitudinally arranged fibrils, which tend to condense around nerve fibers and vessels.⁶⁸ Beyond these fibril condensations, the inter-

stitial areas contain a flocculent matrix that appears to be a residue of the endoneurial ground substance. Endoneurial fibroblasts (Fig. 7-6, B) appear to ramify, forming a number of elongated, attenuated processes. In contrast to Schwann cells and perineurial cells, the endoneurial fibroblasts lack a basal lamina.

It had been suggested that resident endoneurial cells identified as fibroblasts might be macrophages because the latter had been difficult to identify *per se* in normal nerve samples.^{85,86} Subsequent experiments based on intraneural injections of india ink and rat myelin supported endoneurial fibroblasts as a source of phagocytic cells.⁸⁶ More recently, immunocytochemical studies on normal, crushed, and inflamed peripheral nerves in rodents and humans have confirmed the existence of a microglial equivalent in the PNS.⁸⁷⁻⁸⁹ Similarly, immunohistochemical studies have demonstrated macrophages in normal pig peripheral nerve.⁹⁰ Despite the existence of resident cells with phagocytic potential, their numbers clearly can be supplemented quickly by blood-borne elements in disease conditions.

Endoneurial mast cells can be found in most fascicles. Mast cell density in peripheral nerves varies with species and from one nerve trunk to another.⁹¹ Mast cell numbers are increased after nerve transection and in certain diseases of the peripheral nerves;⁹² it appears that mast cells may even play an active role in inflammatory demyelination.⁹³ It is likely that increased mast cells contribute to breakdown of the blood-nerve barrier in inflammatory demyelinating disease, but their functions beyond this will require additional experimental study.⁹⁴

Endoneurial vessels consist of capillaries and venules; lymphatics are lacking. In the peripheral nerves the vascular endothelium is continuous and unfenestrated. A **blood-nerve barrier** has been found in endoneurial vessels that prevents the entry of the blood-borne macromolecules. As in the blood-brain barrier, the basis for the barrier resides in the tight junctions that join the endothelial cells. The effectiveness of the barrier has regional and species variations.^{95,96} Tracer studies consistently have revealed increased vascular permeability at the level of the spinal ganglia. The vessels of the spinal roots, although not as impervious as those in the CNS, are clearly less permeable to macromolecules than those in the sensory ganglia, at least in rats.⁹⁷ Regional and species-related increases in vascular permeability have been proffered as the bases for the radicular and ganglionic localization of certain inflammatory and toxic lesions in laboratory animals, for example, experimental allergic neuritis, diphtheritic polyneuritis, and adriamycin neuropathy.⁹⁸⁻¹⁰⁰ It has been noted, however, that pathogens or toxins may gain access to the endoneurium by first inducing endothelial damage.¹⁰¹ Nevertheless, regional variations in vascular permeabilities may explain the localization of lesions in certain spontaneous diseases, such as canine ganglioradiculitis or neuritis of the cauda equina in horses. Such correlations remain speculative, however, be-

cause the blood-nerve barrier and its variations have not been defined in domestic species. In this regard, it is worth noting that the spinal ganglia and roots of many seemingly normal horses and ponies contain substantial interstitial and perivascular lymphocytic infiltrates. Although these leukocytes may be manifestations of a subclinical ganglioradiculitis, there is little evidence of accompanying neuronal damage in affected ganglia.

Within the peripheral nerve fascicles of horses, ponies, and dogs, it is not unusual to find myxomatous subperineurial structures called **Renaut bodies**. These resemble accumulations of mucous connective tissue,¹⁰² but in humans they have been mistaken for infarcts in the peripheral nerves.¹⁰³ In the horse, these can be identified easily under a dissecting microscope. They appear as elongate, translucent, gelatinous masses. Despite their endoneurial location, they are usually free of nerve fibers. On histological section, Renaut bodies appear as loosely whorled structures (Fig. 7-7) that are rich in amorphous matrix, but relatively poor in cells and collagen. With toluidine blue or cresyl violet, the expansive ground substance stains metachromatically.

At the ultrastructural level, the scattered cells of the Renaut bodies present a spidery or cavitated appearance. The extracellular matrix contains collagenous fibrils that are scattered on a background of very fine flocculent material. The cells of the Renaut body, despite their unusual configuration, resemble fibrocytes. Occasionally, however, they differ in that they have an associated basal lamina. The cytoplasmic cavities seem to form as deep recesses from the cell surface. These membrane-bound recesses may contain collagen fibrils as well as some flocculent residue of ground substance. On immunocytochemical and ultrastructural study, Renaut bodies have been shown to have an elastin filament component as well.¹⁰⁴

Renaut's original theory that these bodies serve a supportive or cushioning function seems to have withstood the test of time. Renaut body formation has been induced experimentally in rats by the mechanical stress of repeated nerve compression.¹⁰⁵ Renaut bodies are also characteristic of nerves subjected to spontaneous forms of compression. In the horse, for example, a subclinical tendinous entrapment of the suprascapular nerve results in local enlargement due largely to profuse Renaut body formation.¹⁰⁶ Rooney¹⁰⁷ described Renaut bodies as edematous basophilic material in the subperineurial space and noted that they increased in the fascicles of the radial nerve in spontaneously induced cases of radial paralysis in horses. Mucoid tissue with a histological composition closely resembling that of Renaut bodies has been encountered in abundance in human and canine forms of hypertrophic neuropathy.^{108,109} This so-called mucoid degeneration has a more diffuse intrafascicular distribution than the subperineurial Renaut bodies, but both forms of myxomatous tissue may appear concurrently in neuropathies.

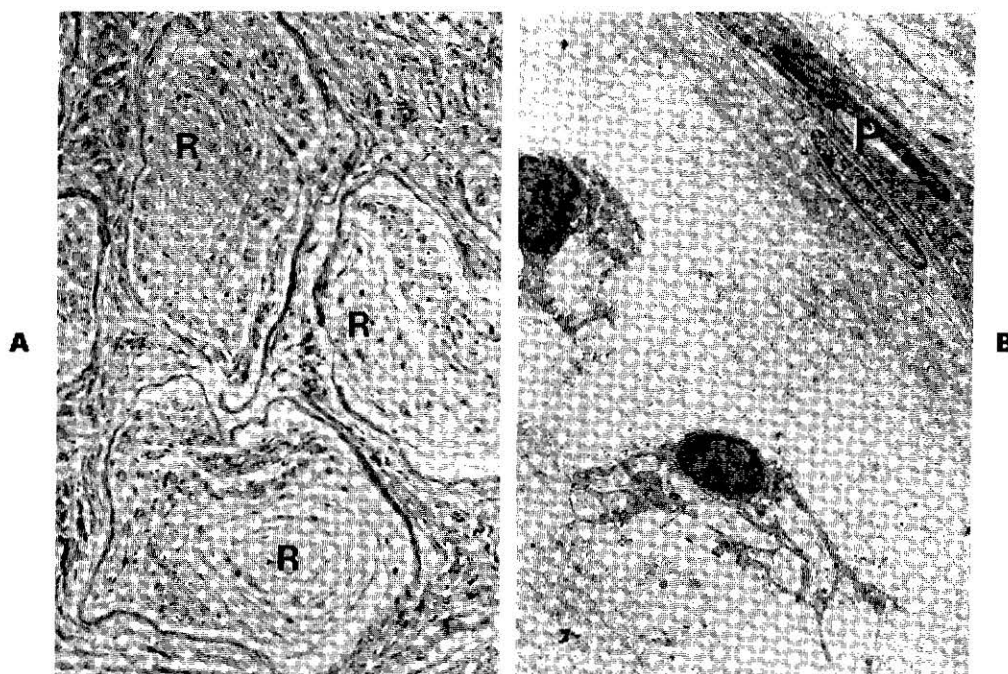


Fig. 7-7. Renaut bodies, horse. **A**, Onion-skin whorled arrangement of transected Renaut bodies (*R*). (H&E, $\times 140$.) **B**, Spidery cell processes and loose metachromatic matrix. Perineurium (*P*). ($\times 3900$.)

The afferent nerve fibers of the PNS originate from cell bodies in the sensory ganglia of the cranial nerves and the dorsal roots. In the latter, the spinal ganglia usually appear as a fusiform or oval swelling on the dorsal root. In ungulates, however, at the segments of the spinal intumescences, the rootlets remain separate rather than fusing to form a single dorsal root. At each segment, these dorsal rootlets are associated with multiple small ganglia,^{110,111} some of which may be partially fused. In the dog and cat, where the dorsal rootlets fuse to form a single dorsal root and ganglion at each segment, the majority of the sensory cell bodies are marginated to the ganglion periphery. Here, the sensory cell bodies form a multilayered cortical region. Fewer cell bodies occur centrally in small aggregates that are separated by prominent longitudinal bundles of nerve fibers.

Except for the bipolar neurons in the spiral and vestibular ganglia, the neuronal cell bodies of the sensory ganglia are typically unipolar. These primary sensory neurons give rise to a single process, an axon stem. The axon stem of many of the spinal ganglionic neurons is elongate and pursues a variably convoluted course around or near the cell body of origin. In the initial convoluted portion, the glomerular segment, even axons of large diameter are not myelinated. Ultimately, the axon stem bifurcates into a central axon that enters the brain or spinal cord and a peripheral axon that terminates distally as a naked axon or in association with a sensory receptor. Earlier claims that multipolar neurons also reside in spinal ganglia were probably based on the crenated appearance of artifactually shrunken neurons.⁸³

In most well-fixed specimens, the size and staining of the sensory cell bodies vary so that one can minimally distinguish small dark and large light neurons.¹¹² Various methods have been used to further divide the ganglionic neurons into subsets with the objective of relating a defined cell type to a specific sensory modality. For example, on the basis of Nissl staining patterns and cell size, Clark¹¹³ identified five types of ganglionic cell bodies in the dog. Because the largest cell bodies with finely granulated Nissl substance closely resembled the neurons of the mesencephalic nucleus of the trigeminal nerve, it was suggested that they subserve proprioception. Small cell bodies were thought to be involved in visceral and pain sensation. More recently, histochemical and immunocytochemical methods have been used to identify subpopulations of sensory cell bodies or their central terminations. The applicability of these techniques may vary among species. For example, primary sensory terminals, presumably nociceptive, can be demonstrated histochemically by their fluoride-resistant acid phosphatase activity in small rodents¹¹⁴ but not in carnivores.¹¹⁵ Similarly, immunocytochemical demonstrations of surface carbohydrate antigens have been used to distinguish certain ganglionic neurons in rats, but these procedures have not been effective in cats.¹¹⁶⁻¹¹⁸ The use of immunohistochemical demonstrations of certain neuropeptides (e.g., substance P (SP), leu-enkephalin, α -neo-endorphin, dynorphin A, cholecystokinin, galanin, somatostatin, vasoactive intestinal polypeptide (VIP), angiotensin I, and calcitonin gene-related peptide) to label sensory neuron subsets seems to be applicable to a wider array of species.¹¹⁹⁻¹²² Certain peptides

are segmentally concentrated in ganglia. For example, in the cat, VIP is present in a much higher percentage of sacral versus lumbar ganglionic neurons (71% versus 34%). The prominence of VIP neurons in sacral ganglia has been correlated with the innervation of the pelvic viscera.¹²³ Attempts to relate the peptide immunoreactivity of a neuron to a specific modality (e.g., SP immunoreactivity and nociception or VIP and visceral reception) should be approached with caution. Such specific cell-peptide-modality correlations have been complicated by demonstrations that a single neuron can be immunoreactive for three and even four peptides.¹²⁴⁻¹²⁶ Moreover, it has been found that the expression of certain peptides in sensory cell bodies can be modified by peripheral axon transection or obstructed axonal transport.¹²⁷ After peripheral nerve injuries, many sensory ganglionic neurons express peptides that they would not normally contain. These injury-induced peptides include VIP, peptide histidine-isoleucine, and galanin.¹²⁸ Nevertheless, in immunocytochemical studies of inherited sensory neuropathies marked by analgesia in various species, there has been consistent reduction of SP, a putative nociceptive transmitter.¹²⁹⁻¹³¹

The neurons of the spinal ganglia contain large, central nuclei with little heterochromatin. The nucleolus is usually prominent and situated centrally. In females, the condensed heterochromatic X chromosome often appears as a nucleolar satellite. The nuclear envelope is rich in pores. In the cytoplasm, the Nissl granules consist of focal accumulations of granular endoplasmic reticulum and closely associated groups of free ribosomes. In the small, dark neurons, free and attached ribosome masses occupy large expanses of cytoplasm, whereas in the large, light cell bodies more discrete ribosomal aggregates are defined by prominent bundles of neurofilaments and tubules.⁸³ Immunocytochemical studies in rats demonstrate that the small, dark neurons react strongly for the 57-KD type III intermediate filament protein, peripherin, whereas the large cell bodies are peripherin-negative but positive for NF-L, the 68-KD neurofilament peptide.¹³² An absence of Nissl granules clearly marks the axon hillock, the site at which the axon stem arises from these unipolar neurons. The hillock and stem are marked by the appearance of closely set microtubules.

In older dogs, the cisternae of endoplasmic reticulum may be distended by clumps of microtubules (Fig. 7-8). These tubules, which measure about 24 nm in diameter, have been found in CNS neurons as well as in the cell bodies of sensory and autonomic ganglia in the dog.¹³³⁻¹³⁶ Although the occurrence of these inclusions has been perceived as age-dependent,¹³³ their appearance in the spinal ganglia of young dogs has been associated with experimentally induced ischemia.¹³⁶ Despite the close resemblance of these intracisternal microtubules to those commonly found in the cytoplasm, the former do not react with antitubulin antibodies and they are not disrupted by vinblastine treatment.¹³⁴ The



Fig. 7-8. Aging change, canine spinal ganglion. Microtubules within endoplasmic reticulum (arrows) of neuron. ($\times 9750$.)

appearance of intracisternal microtubules in sensory neurons in certain cases of ganglioradiculitis again seems nonspecific and perhaps reflects the animal's age.¹³⁷ Focal cytoplasmic aggregates of microtubules also have been identified in the primary sensory neurons of young dogs receiving toxic doses of pyridoxine.¹³⁸

In addition to microtubules, under some circumstances paired helical filaments may be found in the spinal ganglia neurons of dogs. Conglomerates of paired helical filaments with twists every 35 nm are described in the peripheral cytoplasm of sensory neurons of adult dogs subjected to abdominal aortic occlusion.¹³⁹ It was not determined if these fibrillary tangles were a result of the induced ischemia or another metabolic derangement.

Lipofuscin accumulation is a more common manifestation of aging in ganglionic neurons. Cell bodies of aged individuals contain substantial amounts of this golden brown, wear-and-tear pigment. With age these membrane-bound, undigested residues of lysosomal activity increase in both number and size. Their ultrastructure is characteristic in that they consist of dense granular and lamellated material in association with lipid droplets of varying osmiophilia. In addition to these end-stage residues, other lysosomal configurations are encountered, including dense bodies and multivesicular bodies.

Mitochondria in sensory neurons are elongate with shelf-like cristae. Large intramitochondrial granules have been observed in these neurons in laboratory animals.⁸³ The significance of these and rarer crystalline mitochondrial inclusions in equine ganglionic neurons is unclear.

The Golgi complex in sensory perikarya consists of a profuse system of membrane saccules. This membrane complex has a wide perikaryal distribution, which can be dem-

onstrated histologically with silver impregnation or osmic acid staining.

In sensory ganglia, the neuronal cell bodies are ensheathed by **satellite cells** or **amphicytes**. These sheathing cells closely resemble Schwann cells. In this regard, the satellite cells in some species provide the bipolar sensory cell bodies of the acoustic and vestibular ganglia with myelin sheaths.¹⁴⁰ They form a multilaminated capsule of interdigitating cell processes around the cell bodies and the initial or glomerular part of the axon. The interface with the cell body is irregular and marked by cytoplasmic evaginations of the neurons into satellite cell recesses. The satellite cell cytoplasm is electron-dense; profiles of the Golgi complex and endoplasmic reticulum are usually encountered along with lysosomal dense bodies. As with the Schwann cell, a continuous basal lamina is found at the external or abneuronal aspect of the satellite cell. With degenerative changes in the primary sensory neurons, the satellite cells may assume the activities of phagocytes. The satellite cells have the ability to fragment and engulf degenerated neurons.¹⁴⁰⁻¹⁴² In certain pathological conditions, the satellite cell processes may participate in neuronal remodeling by invaginating the neuronal perikaryon and sequestering portions of the peripheral cytoplasm that contain a whorled membranous configuration.¹⁴³ In certain sensory neuronopathies of the dog, we have observed ultrastructural images that suggest the satellite cells remove marginated membranous bodies from sensory cell bodies. Similar images also have been seen on rare occasions in the ganglia of normal dogs. It appears that satellite cells may provide a means, in addition to autophagy, to rid the neuron of effete membrane.

In equine spinal ganglia, the satellite cells seem particularly abundant. They commonly form large, eccentric accumulations in relation to the initial or glomerular segment of the axon.¹⁴⁴ On tangential section, these accumulations may simulate the appearance of **Nageotte nodules**, that is, the focal proliferations of satellite cells that form at the sites of sensory cell body loss.

Not all of the primary sensory neurons are confined to ganglia. In **domestic animals**, solitary cell bodies are found scattered in the ventral roots.¹⁴⁵ It had been suggested that these aberrant cell bodies were the source of sensory fibers, which, in conflict with the Bell-Magendie law, travel centrally in the ventral roots. Fiber degeneration after spinal ganglionectomies in cats,¹⁴⁶ however, indicates that the afferent unmyelinated axons in the ventral roots originate from cell bodies in the spinal ganglia. It has been suggested that some C fibers in the ventral roots are nociceptive, and their presence could explain why dorsal rhizotomies may fail to relieve pain.^{147,148} Nevertheless, demonstrations of a distal-proximal decline in the proportions of C fibers in the ventral roots indicate that most afferent fibers form recurving loops and do not enter the spinal cord via the motor roots.¹⁴⁹ Retrograde transport studies¹⁵⁰ also support an eventual dorsal root entry for the afferent fibers of the ventral roots.

The somatic motor neurons of the peripheral nervous system originate from cell bodies in the ventral horns of the spinal cord and from the brain stem motor nuclei of certain cranial nerves. The cranial motor components include the nuclei of cranial nerves III, IV, V, VI, VII, and XII, as well as the nucleus ambiguus.

The α -motor neurons are among the largest in the nervous system. These multipolar neurons appear polygonal and contain abundant Nissl substance. The latter consists of distinct flakes that fill the perikaryon and extend into the dendritic origins. The nucleus is large, spherical, and central; it contains a prominent lacy or vacuolar nucleolus but little heterochromatin. In females, a proportion of motor neurons will contain discernible **Barr bodies**. The Barr body represents a genetically inactive or condensed X chromosome. This small heterochromatic mass of sex chromatin usually appears as a basophilic nucleolar satellite.

In the spinal cord, the α -motor neurons reside in the regions of the ventral horn, which Rexed^{151,152} identified as lamina IX and X. The large axons emanating from the somatic motor neurons traverse the ventral funiculus in small bundles to enter the ventral rootlets. It is in the rootlets that the central-peripheral nervous system transition zone occurs. This transition zone undergoes striking change in various spinal cord and peripheral nerve diseases in which there is damage to radicular myelinated axons.¹⁵³ In response to such damage, there is a glial outgrowth from the spinal cord into the roots. The astroglial bundles that form in the roots are a characteristic but nonspecific reaction seen in various human diseases, including polyradiculoneuritis and the spinal muscular atrophies. The axons of the somatic motor neurons divide most extensively in their distal course to supply multiple muscle fibers. The motor neuron and all the muscle fibers it innervates constitute a **motor unit**. Motor units vary widely in size, that is, in the numbers of muscle fibers supplied by a single neuron. There may be as few as 10 and as many as 1000 or more skeletal muscle fibers innervated by a single motor neuron.¹⁵⁴

It has been demonstrated repeatedly in mammals that the α -motor neurons are somatotopically organized within the ventral horns.¹⁵⁵⁻¹⁶⁰ Motor neurons innervating axial muscles are localized in medial cell groups that extend over the length of the spinal cord. The cell bodies supplying appendicular muscles are arrayed in columns in the cervical and lumbosacral intumescences, where they bring about the characteristic lateral flare of the ventral horn. In the intumescences, the neurons supplying the proximal muscles of the limbs are located cranially and ventrally; those innervating the distal muscles of the limb are situated more caudally and dorsally. The pools of motor neurons to flexor muscles are situated lateral to those supplying the antagonistic extensor muscles. Knowledge of these somatotopic arrangements allows greater precision in localization of spinal or root lesions in accordance with patterns of limb muscle weakness and wasting.

Multiple dendritic stems originate from each α -motor neuron, and these arborize in different directions. The arborizations are extensive in lamina IX and extend dorsally in laminae VIII and VII. These extensive dendritic arborizations, along with the soma, form a vast receptive area for each α -motor neuron. They receive diverse inputs, which can be demonstrated in the varied ultrastructure of the axon terminals or **boutons**. These boutons are mostly densely arrayed in synapses on the distal branches of the dendritic tree. Whereas the α -motor neurons receive some direct projections from primary sensory neurons and from the cerebral cortex via corticospinal projections in some animal species (primates, raccoons, dog), most descending and segmental projections are derived from interneurons in domestic species.^{161,162}

In addition to the somatic motor neurons, the ventral horns also contain the cell bodies of the γ -efferent neurons, which provide the motor innervation of intrafusal fibers of the muscle spindle. The γ -efferent axons originate from smaller cell bodies within the ventral horns. The γ -motor neurons contain smaller nuclei than the α -motor neurons, and the nucleoli are small, dark, and compact. The classification of intermediate-sized spinal motor neurons into α and γ subsets may be accomplished on the basis of differential ultrastructural criteria. These criteria include synaptic bouton types, synaptic frequencies, and nucleolar configuration.¹⁶³ Some spindles may be innervated by branches from the motor axons to extrafusal muscle fibers. The latter originate from skeletal-fusimotor or β -neurons. It may be that the β -neurons correspond to smaller α -neurons with unusually low synaptic frequency.¹⁶³

Besides the axons stemming from the motor neurons of the ventral horn, the ventral rootlets also contain preganglionic sympathetic fibers in the thoracic and first few lumbar segments and preganglionic parasympathetic fibers in the sacral segments. The thoracolumbar outflow originates from medium-size, multipolar neurons in Rexed's lamina VII or the zona intermedia. The cell bodies are not confined to the metameric nucleus intermediolateralis as illustrated in most textbooks; they also extend medially from this nucleus through the zona intermedia up to the region of the central canal. These more medially situated cells reside in the intercalated and paracordal nuclei.¹⁶⁴⁻¹⁶⁶ Similarly, the cell bodies giving rise to the parasympathetic outflow from the sacral segments are not limited to the nucleus intermediolateralis. Retrograde labeling studies have identified sacral preganglionic neurons that extend into the ventral horn and others that are scattered medially in the zona intermedia.¹⁶⁷

The preganglionic neurons of the parasympathetic or craniosacral outflow project to synapse on cell bodies in ganglia that are situated in or near the organ receiving the postganglionic innervation. The preganglionic sympathetic neurons leave segments of thoracolumbar spinal cord to synapse on cell bodies in prevertebral ganglia (e.g., celiac

or cranial mesenteric ganglion) or paravertebral ganglia (i.e., the sympathetic chain ganglia). A great many autonomic ganglia are small and can be identified only microscopically along the course of various nerves. These go unnamed.

In general, the neuronal cell bodies in autonomic ganglia are smaller and range less in size than those in sensory ganglia.¹⁶⁸ In the sympathetic ganglia of the dog and cat, Cajal¹⁶⁹ observed two populations of neurons: large cells that varied from 40 to 60 μm in diameter and smaller cells that ranged from 20 to 28 μm . Within ganglia, nests of neuronal cell bodies are separated by fascicles of small myelinated and unmyelinated axons. In contrast to sensory ganglia, autonomic ganglia contain multipolar rather than unipolar neurons. These motor neurons are encapsulated by satellite cells, but the dendrites from the perikarya project through their capsules to ramify within the ganglia. Using silver impregnation, Cajal¹⁶⁹ demonstrated that sympathetic neurons varied in their pattern of dendritic arborization and could be subdivided on this basis. Preganglionic fibers usually form axodendritic synapses en passage while running parallel or winding around the dendrites of the ganglionic neurons.¹⁷⁰ Axosomatic synapses are relatively infrequent. The dendrites commonly contain small clusters of vesicles (30-50 nm), which are believed to hold stores of catecholamines. In addition to preganglionic fibers, sympathetic neurons are synaptically contacted by substance P-containing collaterals of sensory fibers originating in the spinal ganglia and terminating in the gastrointestinal tract.¹²²

Normal canine sympathetic neurons have been subdivided on the basis of the staining and arrangement of Nissl substances.¹⁷¹ After staining with a basic dye, three types were identified: (1) large cells with deeply stained and uniformly disposed Nissl substance, (2) neurons with Nissl substance condensed at the periphery, and (3) cell bodies with very fine, weakly stained granules distributed throughout the cytoplasm. Cells in which the Nissl substance is very fine or condensed at the periphery may simulate the appearance of neurons undergoing central chromatolysis.¹⁷² This chromatolytic appearance can be quite convincing in ganglia of normal dogs and horses wherein relatively large numbers of neurons also contain eccentric nuclei. In addition to Nissl staining, subtypes of sympathetic ganglionic neurons can be distinguished by their content of neuropeptides, for example, somatostatin, vasoactive intestinal polypeptide, and neuropeptide Y. Many of the neurons that are immunoreactive for somatostatin and neuropeptide Y are noradrenergic, whereas most of the VIP-positive neurons are not noradrenergic in the guinea pig.¹⁷³

In humans and in the rabbit, significant numbers of sympathetic neurons contain two or more nuclei.^{112,169} Multinucleate cells seem to be less common in domestic mammals. Multiple nucleoli, however, are frequently seen in the sympathetic neurons of these species.

Just as in the case of the sensory ganglia, the range of

normal and age variations is difficult to assess in autonomic ganglia. In apparently normal dogs and horses, vacuolated neurons are described in sympathetic ganglia.^{174,175} These vacuoles commonly are large so that they occupy much of the perikaryon and displace the nucleus. In human autonomic ganglia, vacuolated neurons increase with various diseases of the blood vessels, heart, intestine, and larynx.¹¹² Pseudovacuaes also have been described; these result from the retraction of the neuron from the surrounding satellite cell.¹⁷⁶ In the autonomic ganglia of mature horses, the large vacuoles in the ganglionic neurons may contain pale eosinophilic material. Electron microscopic study indicated that these membrane-bound vacuoles are formed by distension of endoplasmic reticulum. These markedly enlarged cisternae contain a finely granular or flocculent substance that, when preserved, is lightly stained with eosin.¹⁷⁷ These equine inclusions seem to have many features in common with the colloid inclusions that are described in the hypoglossal and other motor neurons in older human beings.^{178,179}

Occasionally we have also observed 8- to 15- μ m osmiophilic inclusions in the nerve fibers within equine prevertebral autonomic ganglia. These inclusions correspond ultrastructurally to large spheroidal swellings of scattered unmyelinated axons that were filled with diverse membranous bodies and mitochondria. The significance of these axon swellings and others seen occasionally in equine enteric ganglia remains unclear. The spheroids found in the sympathetic ganglia appear identical ultrastructurally to the dystrophic axons found in the equine dysautonomia known in Europe as grass sickness.¹⁸⁰ Dilated axons containing a variety of organelles have also been found in prevertebral autonomic ganglia of aged rats¹⁸¹ and human beings.¹⁸² In the rodent and human age-related axon dystrophy, the swellings appeared to be more often terminal or preterminal than in the horse. It has been suggested that these changes may represent a degenerative alteration of the normal turnover and regeneration that continually operate at the axon terminal.¹⁸²

Just as with the spinal ganglia of apparently normal horses and ponies, lymphocytic aggregates appear also in the capsules and substance of equine sympathetic ganglia. In one study of an Argentinean disease similar to grass sickness, these lymphocytic infiltrates were found in the perineurial sheaths of the celiacomesenteric ganglia of three of four control horses.¹⁸³ These mononuclear cells often appear to be aggregated in perivascular or capsular arrays, although more diffuse infiltrates are also present. These are only occasionally associated with obvious neuronal damage. It remains problematical whether these are manifestations of a prevalent, subclinical ganglionitis or if they are, perhaps, usual sites of mononuclear cell extravasation, not unlike the milky spots of serous membranes.

In addition to the aforementioned "vacuoles," other cytoplasmic and nuclear inclusions have been identified in sympathetic neurons of seemingly normal domestic animals.

In the dog these may include intracisternal microtubular inclusions like those found within the granular endoplasmic reticulum of sensory ganglionic neurons¹³⁴ and large, round, oval, or rod-shaped perikaryal accumulations of glycogen.¹⁸⁴ These PAS-positive, amylase-degradable deposits, which were similar to those seen in the glycogenoses, measured up to 28 μ m and were also found in neuronal processes. In the horse, ultrastructural studies have disclosed the presence of electron-dense neuromelanin within lipofuscin granules of sympathetic neurons.¹⁸⁵ Various types of intranuclear inclusions have been identified ultrastructurally in normal feline sympathetic neurons: circular, granular nuclear bodies that are separated by a halo from the nuclear matrix; fibrillar fascicles or intranuclear batonnets consisting of tubulofilamentous inclusions or microfilament spindles; crystalloid microtubules; and lacunar bodies formed of perichromatin granules and fibrils.^{186,187} Knowledge of these neuronal inclusions and variations can prevent confusion in evaluating putative disease changes in autonomic ganglia.

In examining the sympathetic ganglia microscopically, one may encounter clusters or nests of neuroendocrine or paraganglionic cells that appear poorly stained with basic dyes.¹⁸⁸ These pale, polygonal neuroendocrine cells, which are also known as small granule-containing cells and small intensely fluorescent or SIF cells, are accompanied by flattened supporting cells. These aggregates may be very prominent in equine ganglia. Based on the content of specific granules, four types of small granule-containing cells have been identified in autonomic ganglia. These paraganglionic cells produce biogenic amines and receive cholinergic synaptic innervation. Type I cells are believed to serve as inhibitory interneurons in the ganglia and types II to IV may serve as neuroendocrine cells with local paracrine and generalized blood-borne endocrine effects.¹⁸⁹ It appears that paraganglionic cells can modulate the activity of sympathetic neurons.¹⁹⁰

References are on page 481.

GENERAL PATHOLOGY OF THE PERIPHERAL NERVOUS SYSTEM

- Traumatic lesions of the peripheral nervous system
- The axonal reaction
- Wallerian degeneration
- Degeneration and regeneration of unmyelinated axons
- Distal axonopathy
- Segmental demyelination and its consequences

This section is intended to provide an overview of the range and chronology of the reactivities of the structural elements of the PNS to various types of insult. We have elected to include a discussion of the axonal reaction here, although it involves central as well as peripheral somata.

Traumatic lesions of the peripheral nervous system

In domestic animals, trauma is considered the most common cause of peripheral neuropathy¹ and nerve injury the most frequent cause of neurogenic muscle wasting.² The forms of nerve trauma are diverse and include pressure, stretching, mechanical blows, and fractures. Iatrogenic injuries may result from surgery, application of casts or splints, and hypodermic injections.

Mechanical injury can induce temporary or permanent motor and/or sensory deficits, depending on the nature and site of the lesion and the likelihood of functional repair. Seddon³ identified three types of nerve lesions of mechanical origin. In most spontaneous injuries, a mixture of these types would be expected, rather than an exclusive occurrence of one.⁴ **Neuropraxia**, a result of mild injury, designates a localized block in conduction without degenerative changes in the nerve fibers. The prognosis is good because there is preservation of axons, and functional restoration occurs in a matter of days or weeks. The term **axonotmesis** is applied when the damage interrupts axons but spares the connective tissue stroma of the nerve. Wallerian degeneration ensues, but subsequent axon regeneration may lead to substantial restoration of function because there is no disruption of endoneurial elements and presumably the Schwann cell basal laminae. **Neurotmesis** describes injuries in which partial or complete transection of the nerve leads to Wallerian degeneration. With this more disruptive type of injury, recovery is compromised as regenerating fibers often fail to be properly routed to re-establish functional endings.

Many forms of direct injury to a nerve result in axon degeneration, whereas compression is more likely to produce focal demyelination with conduction block. Prolonged or severe compression is likely to be followed by some Wallerian degeneration. With repeated or chronic compression, onion bulbs are likely to form with recurring demyelination and remyelination.⁵

In the domestic species, certain nerves are predisposed to injury by virtue of (1) superficial locations, (2) proximity to primary bone or joint abnormalities, (3) dystocia correction procedures, and (4) proximity to injection sites.

The axonal reaction

Interruption of peripheral axons is a common result of injury, and it engenders a sequence of retrograde and anterograde responses. There are changes proximal to the interruption both in the stumps of the severed axons and in the cell bodies of origin. The retrograde response in the neuronal cell bodies is called the **axonal reaction** or **central chromatolysis**. The nature of the signal for this retrograde cellular adaptation to injury is unclear. Many theories have been suggested.⁶ Among the more plausible is loss of a postsynaptic trophic factor or loss of a neuronal repressor substance. Although loss of a target-derived, trophic substance such as nerve growth factor (NGF) has been suspected, it clearly is not solely responsible.⁷ Both the bul-

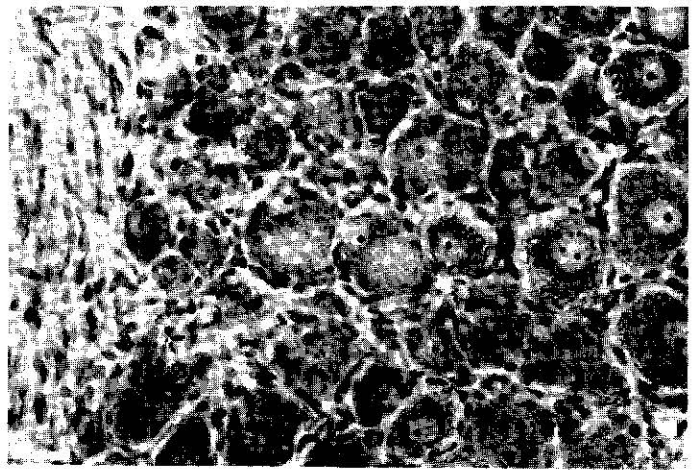


Fig. 7-9. Axonal reaction, dog. Following section of the greater splanchnic nerve, two neurons in a spinal ganglion show the axonal reaction. Neuron on left has a nuclear cap. (Luxol fast blue, cresyl echt violet, $\times 350$.)

bospinal α -motor neurons and the sensory neurons of the cranial nerves and spinal ganglia undergo similar chromatolytic changes. Axotomized γ -motor neurons, however, undergo no chromatolytic changes that are detectable with the light microscope.⁸ Chromatolytic changes may be discerned as early as 2 or 3 days after injury, but usually are most pronounced after 1 to 3 weeks.⁹ Typically the neuron cell body becomes swollen with rounded contours, although there may be a reduction in the dendritic membrane area.¹⁰ The basophilic Nissl bodies in the cell center are reduced to a fine, dust-like material so that a central pallor develops (Fig. 7-9). In motor neurons, the nucleus often assumes an eccentric position opposite the axon hillock, but in primary sensory neurons the nucleus is located close to the axon root. The nuclear margination may be so marked as to appear as a protrusion from the cell. The nucleolar volume is increased. The nuclear outline is irregular, and a basophilic cap composed of polysomes and short lengths of rough endoplasmic reticulum (rER) may appear on the cytoplasmic aspect of the nucleus.^{8,11} In females, the sex chromatin or Barr body is displaced from its usual paranucleolar position.

Central chromatolysis is an anabolic response in which heightened nuclear RNA synthesis is followed by increased cytoplasmic RNA content and elevated protein synthesis. At the ultrastructural level, chromatolysis is represented by a disintegration of the focal concentrations of rER that together with free polysomes form the **Nissl bodies**. The cisternal arrays are replaced by short, flattened or vesicular membrane profiles. In some studies, a proliferation of narrow cisternae devoid of ribosomes is described in the peripheral cytoplasm. These stand in continuity with the rER and are identified as subsurface cisternae.¹² With the breakdown of Nissl aggregates, the ratio of free to membrane-

bound ribosomes becomes greatly increased. The marked increase in free polyribosomes has been correlated with heightened and selective synthesis for restoration of the axon.¹³ There is a change in gene expression toward the early developmental program so that synthesis of tubulin and actin increases, but neurofilament protein declines.¹⁴ It has been suggested that these changes in gene transcription may be regulated through transactivating proteins in the nucleus. Demonstrations of early postaxotomy increases in some nuclear proteins and decreases in others tend to support this suggestion.¹⁵

Besides the striking ultrastructural changes in the rER, there is an increase in lysosomes that correlates with histochemical demonstrations of elevated acid phosphatase activity. The Golgi apparatus undergoes peripheral displacement, that is, retispersion, along with dispersion of the Nissl bodies in reactive cell bodies.^{12,16} Whereas some studies report a mitochondrial increase during central chromatolysis, others have found a redistribution and hypertrophy of these organelles.⁹ Variable perikaryal increases in neurofilaments and tubules have also been noted. Following axotomy, there is enhanced phosphorylation of neurofilaments in the affected perikarya, and this has been associated with diminished transport of the filaments into the axon.¹⁷ Moreover, there is a reduction in the levels of mRNA for neurofilament peptides after axotomy. This depression, which persists for about 6 weeks, may be responsible to some extent for the slender diameters of regenerating axons. The subsequent recovery of normal axonal diameter is temporally associated with rebounded and increased levels of NF mRNA.¹⁸ Perikaryal synthesis of **peripherin neurofilaments** as measured by levels of mRNA is doubled after axotomy and thus parallels the increased expression of tubulin and actin.¹⁹

In the brain stem and spinal cord, glial proliferation accompanies the reaction of the motor neurons. Microglia (type III glial cells) proliferate quickly and cover large expanses of the neuronal and dendritic surfaces. In rodents, microglia separate terminal boutons from the surfaces of cranial motor neurons.^{20,21} In the cat, axotomy results in substantial loss of synapses from spinal α - and especially γ -motor neurons, but the accompanying microglia increase is not associated with removal of synaptic terminals.⁸ Synaptic stripping from axotomized motor neurons may prove beneficial in promoting axon regrowth by diverting neuronal energy from neurotransmission toward regeneration.²² The close apposition of microglia and neurons may also facilitate the transfer of neuronotrophic factors that could stimulate neuron recovery. In the case of retrograde neuronal death, the microglial population doubles, and these cells phagocytose the degenerated neuropil.^{23,24} Astroglia also increase in prominence to ensheath the axotomized neuron.²⁵ Oligodendroglia, by contrast, seem to undergo no perineuronal alteration in the wake of axotomy.

The aforementioned changes are typical of those occur-

ring in the neurons that form the projections of the PNS, and they are usually associated with axon regeneration. Yet lesions of the trigeminal nerve branches and peripheral nerves in rats and kittens have resulted in transganglionic degeneration of sensory fibers in the brain stem and spinal cord.^{26,27} This degeneration of the central projections of the primary sensory neurons, however, has been associated with substantial retrograde degeneration of sensory ganglionic cell bodies.²⁸ Interruption of axons that project entirely within the CNS has a high probability of eventuating in regressive perikaryal changes.¹³ The changes are variable. Some somata react dramatically and undergo rapid degeneration; others undergo retrograde atrophy²⁹ and persist in shrunken form.

The appearance of the axonal reaction varies with age, species, type of neuron, the nature of the inciting lesion, and its proximity to the cell body. Axotomy in young animals evokes changes that are abrupt and more severe than those that occur in adults. Injury to axons in neonates is far more likely to cause death and disappearance of neurons than in adults.⁹ Studies of axotomy during late prenatal and early postnatal life suggest the ensuing compaction and segregation of the neuronal nucleolar components are related to inhibition of ribosomal RNA synthesis and inactivation of protein synthesis.³⁰ These changes contrast with the nucleolar hypertrophy that follows axotomy in the adult. The death of sensory cell bodies in the spinal ganglia that commonly follows axotomy in the rat has been prevented by application of NGF to the proximal stump.³¹

Torvik¹¹ has reviewed the substantial variations that occur among the rat, mouse, and rabbit in the axon reaction as provoked by crush lesions of the facial nerve. Along this line, it is interesting to note that Cammermeyer³² found that peripheral rather than central chromatolysis developed soon after facial nerve transection in the mouse. In our experience, peripheral chromatolysis has been a more usual finding in spontaneous motor neuron diseases or neuronopathies. Interruption of the axon proximally provokes a more rapid and severe reaction than a distal lesion. Relatively mild peripheral nerve lesions (i.e., those induced by crush) are less likely to cause degeneration and loss of neurons than nerve avulsions or resections performed in proximity to the cell body.^{9,33} In this regard, it has been shown in the hypoglossal neurons of the cat that the synaptic detachment that typically follows nerve transection does not occur after nerve crush.³⁴

Although central pallor in the neuron is the anticipated axon reaction, interruption of peripheral axons proximally and traumatically in neonates may produce totally achromatic cell bodies.²³ At the ultrastructural level, such achromatic neurons contain electron-lucent cytoplasm, which is depleted of organelles. These cells are destined to die.⁹ The increased vulnerability of these neurons has been attributed to an inability of immature neurons to mount a chromatolytic response and to a greater dependence on tro-

phic factors produced at the periphery.³⁵ By way of contrast, hyperchromatic neurons may appear after the chromatolytic response to peripheral axon injury. These basophilic neurons with densely packed Nissl granules signal the recovery phase of the axon reaction.³⁶ Long-term studies of rat motor perikarya giving rise to regenerated axons 10 months to a year after axon interruption revealed that these cell bodies were actually enlarged with more strikingly prominent dendrites than control neurons. It has been suggested that this perikaryal enlargement may reflect increased metabolic demands placed on the cell body by persistent remodeling of the regenerated myelinated axon.^{35,37}

Wallerian degeneration

Peripheral nerve transection or crush results in degeneration of myelinated and unmyelinated axons distal to the point of interruption. The process that is called **Wallerian degeneration** begins in myelinated fibers with slight retraction of the myelin at the nodes of Ranvier. Sequential study indicates that regressive changes may be noted in the axoplasm before they can be identified in the myelin sheath.^{38,39} Twelve to 36 hours after the insult, the myelin internodes begin to segment into linear series of **ellipsoids**. The segmenting constrictions that define the ellipsoids and correspond to regions of axon narrowing form at the Schmidt-Lantermann incisures.⁴⁰ Although early studies indicated numerical increase of incisures in the internodes, more recent studies have found only an increased promi-

nence of existing incisures.^{41,42} The swellings within the internodal myelin had been thought to result from Schwann cytoplasm invasion at the incisures,⁴³ but the swelling actually is caused by peri-incisural dilations at the intraperiod lines. The cytoplasmic spirals of the incisures are relatively stable structures and remain intact as the ellipsoids form by segmentation.⁴⁴ The initiation of axonal breakdown in Wallerian degeneration is dependent upon early recruitment of hematogenous macrophages.⁴⁵ Interference with recruitment of macrophages into the nerve results in prolonged survival of the axons after neurotomy. It appears that a positive signal originating from degenerating axons induces myelin sheath breakdown.⁴⁶ The resulting ellipsoids, which Cajal identified as **digestion chambers**, contain central axon fragments within ovoids of degenerated myelin (Fig. 7-10).

The basal lamina around the disintegrating myelin and axon persists. With axon degeneration, Schwann cells cease production of myelin membrane components. Cessation has been correlated with a down-regulation of myelin structural protein gene transcription.⁴⁷ Mitotic proliferation of Schwann cells in the distal stump is initiated 2 days after the insult. This proliferation is greater in nerves containing many large myelinated axons than those with mostly smaller fibers.^{48,49} Studies in the cat with tritiated thymidine have demonstrated a sevenfold increase in Schwann cell labeling in the distal nerve stump versus intact control nerves.⁵⁰ The premitotic incorporation of ³H thymidine spreads from proximal to distal in the stump at a velocity of 199 mm/day,

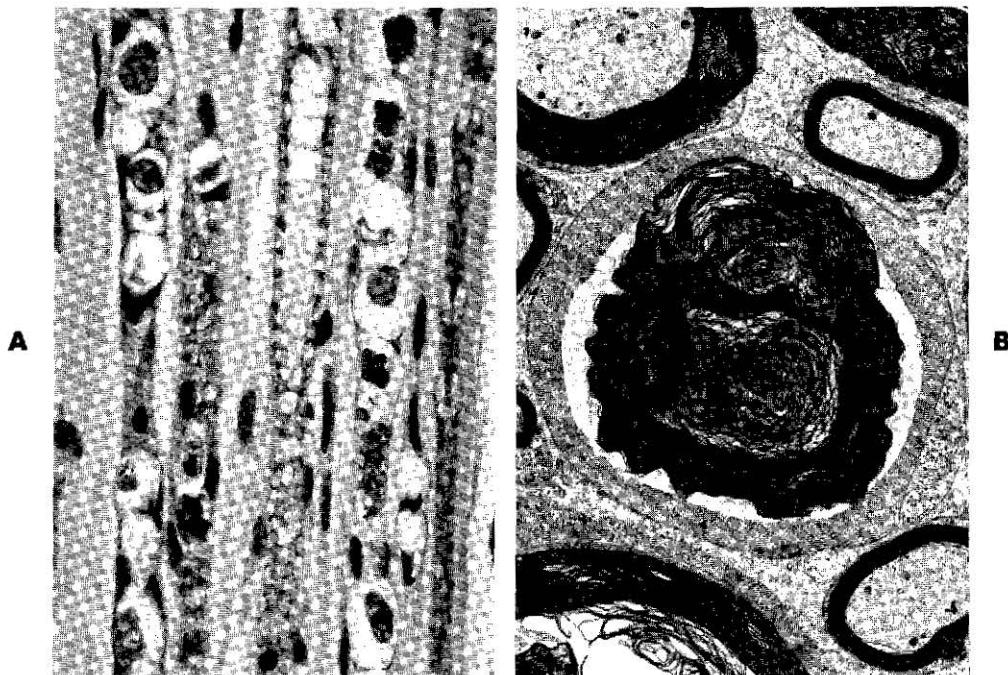


Fig. 7-10. Wallerian degeneration, horse. **A**, Chains of digestion chambers with myelin debris. (H&E, $\times 560$.) **B**, Myelin ovoid. ($\times 5625$.)

suggesting that rapid axonal transport may be involved in some way in the anterograde Schwann cell mitotic response.⁵¹ It also has been suggested that during degeneration, Schwann cells through contact come under the demonstrated mitogenic effect of the exposed axolemma.⁵² The proliferating Schwann cells, some of which grow out of the distal stump, are delimited by the persisting basal lamina and associated endoneurial collagen.^{53,54} In the distal stump this proliferation forms longitudinal cords of Schwann cells called **Büngner's bands** (Fig. 7-11). Proliferation of perineurial cells around fascicles in the distal stump also has been observed 3 to 6 days after crush injuries.⁵⁵ Myelin disintegration continues as the Schwann cells proliferate. Myelin debris and lipid droplets may appear within the Schwann cells⁵⁶ soon after the onset of degeneration. The origin of the phagocytes that remove most of the degenerative debris has been reported variously. The relative importance of Schwann cells and macrophages in the clearance of debris has been difficult to define on purely histological bases.⁵⁷ For example, some investigators^{38,39,58,59} concluded that myelin removal was largely an autodigestive process on the part of the Schwann cell, whereas others^{60,61} found that macrophages of hematogenous origin played the major role in eliminating myelin debris. The latter observation has been supported by experimental studies on mouse nerves enclosed in millipore diffusion chambers, which have shown that elimination of myelin debris is dependent upon invasion of hematogenous cells.⁶² This influx of macrophages is the second wave of hematogenous cell recruitment, and it is later and larger than the first, which initiates axon breakdown.⁶³ In vitro studies of cat sciatic nerve explants⁶⁴ revealed a degeneration sequence in which the Schwann cells reject the myelin. This myelin rejection was followed by proliferation of the liberated Schwann cells within the basal lamina and release of fragmented myelin debris into the endoneurium via breaks in the surrounding basal lamina. The degenerating myelin and Schwann cells behaved as separate components; while the Schwann cells formed bands of Büngner they were not involved in phagocytosis or degeneration of myelin. It has been suggested, however, that because myelin-forming Schwann cells become MHC II-positive after nerve crush, they may present some component of the myelin to macrophages, which then digest and remove it.⁶⁵ The removal of the lipids derived from degeneration progresses more rapidly in younger than older individuals.⁶⁶

Regenerative terminal and collateral axon sprouting occurs soon after nerve interruption. Sprouts from the expanded proximal ends of the interrupted axons may appear as early as 2 days after injury,⁶⁵ although earlier studies did not find sprouting until 4 days.⁵³ If the proximal and distal nerve stumps are closely approximated as with a crush type of injury, reinnervation is likely to be effected. The wider the gap between the stumps, the greater the likelihood that the sprouts will be misdirected.⁶⁵ It is well established that

the distal stump exerts a neurotrophic influence,⁶⁷ the regenerating neurites traverse the injured region or gap with accompanying Schwann cells from the proximal stump,⁶⁸ and they enter the Büngner's bands in the distal stump. Thus, the individual bands contain multiple axon sprouts that grow distally at a rate of 1 to 2 mm/day. The cellular bands that are defined and oriented by basal laminae serve as conduits for the elongating sprouts as they progress to the periphery. In older individuals, the steps that lead to regeneration are delayed, and the survival of proliferated sprouts is diminished.⁶⁹

Much remains to be learned about the trophic and extrinsic guidance factors that encourage axon regeneration. It has been suggested that increased permeability of the blood-nerve barrier after the induction of Wallerian degeneration may permit access of blood-borne neurotrophic substances.⁷⁰ Recent work on a **growth-associated phosphoprotein, GAP 43**, found in growth cones of developing and regenerating axons, suggests that it affects the rate at which membrane is added to outgrowing neurites.⁷¹ The Schwann cells appear to produce neurotropic and neurotrophic factors for the growing axons, such as **nerve growth factor (NGF)** and **ciliary neurotrophic factor (CNTF)**.^{72,73} Reactive Schwann cells produce NGF, and it has been suggested that they sequester this peptide on induced NGF receptors on their surface, thus providing a substrate for the growth of NGF-dependent axons.⁶⁵ Yet, studies in the rat surprisingly have demonstrated a distinct reduction in axonal transport and retrograde transport of NGF after axotomy and during regeneration.⁷⁴ Also there is lack of retrograde transport of CNTF.⁷³ Besides NGF and CNTF, other putative neurotrophins for axon regeneration have been identified, including leupeptin, a protease inhibitor, and glia maturation factor β , an endogenous nervous system protein.^{75,76} The regenerative process is associated with substantial loss of volume of the proximal axon as increasing amounts of radiolabeled material are delivered distally to the regenerating end of the axon.⁷⁷ The initial appearance of multiple small sprouts within a Büngner's band may resemble that of normal unmyelinated axons. Myelination of some of the sprouted axons, however, begins as early as 7 days after nerve damage,⁵³ and with time the proportion of myelinated axons in the regenerating units increases.⁷⁸ The spreading of Schwann cells along the regenerating axons and the ensheathing may be mediated by contact with basal lamina constituents, that is, collagen type IV, laminin, heparan sulphate, and the like.⁶⁵ It is believed that the multiple axon sprouts in a single reinnervated Büngner band are derived from the regenerating activities of a single myelinated axon.⁷⁸ These regenerating units are at first tightly arranged and appear on transverse section as a compact group of Schwann cell processes with multiple sprouts. Each hyperinnervated band is encircled by a continuous basal lamina. Later, individual regenerating units become less compact as gaps develop between the component axon/Schwann ele-

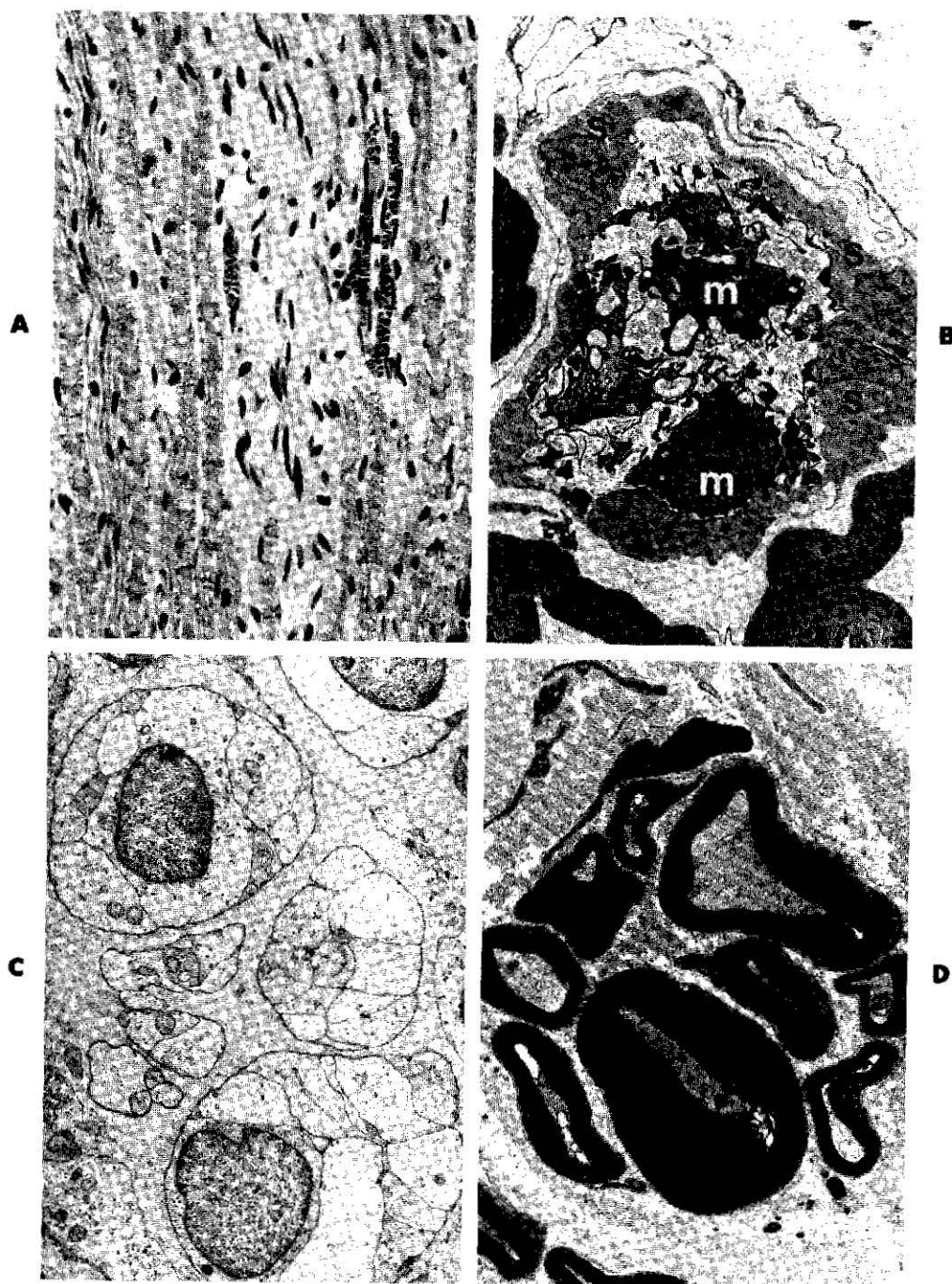


Fig. 7-11. Wallerian degeneration. **A**, Büngner's bands: cords of proliferating Schwann cells, horse. (H&E, $\times 350$.) **B**, Macrophages (*m*) infiltrate a cord of proliferating Schwann cells (*s*), horse. ($\times 3750$.) **C**, Büngner's bands. Transected fascicles of Schwann cells, horse. ($\times 5625$.) **D**, Cluster of myelinated axon sprouts, dog. ($\times 5625$.)

ments. The clusters that form from subdivision of the regenerating units consist of axon-Schwann elements that are separated by small amounts of endoneurial collagen. The slightly separated axon-Schwann units in a cluster commonly lack an intact encircling basal lamina.⁷⁸ Supernumerary axon sprouts—those that do not participate in the restoration of the peripheral innervation—undergo regression. The myelinated axons that re-establish innervation have a normal 1:1 internodal relationship with Schwann cells, but the regenerated internodes, despite extensive remodeling of myelin, are shorter than the originals, and the axons are of lesser diameter. Axonal diameter reduction often is disproportionately less than internodal length shortening.³⁵

Degeneration and regeneration of unmyelinated axons

Wallerian-type degeneration of unmyelinated axons—the so-called fibers of Remak—cannot be clearly resolved with routine light microscopic procedures. The degeneration and subsequent regeneration have been defined, however, using the electron microscope.⁷⁹⁻⁸³ Following nerve transection or crush, degeneration of unmyelinated fibers progresses rapidly. By 24 hours, prominent axonal swellings develop immediately proximal and distal to the point of injury. These enlargements contain accumulations of mitochondria and lamellar membranous configurations. Farther distal to the point of interruption, the first indication of axon degeneration appears within 24 hours as a loss of neurotubules. This is soon followed by breakdown of the endoplasmic reticulum, granular disruption of neurofilaments, variable axon swelling, and finally axolemmal disintegration.⁸² By 2 or 3 days, many unmyelinated axons have already disappeared.^{79,81} The degeneration and disappearance of affected axons are not synchronous; in one study⁸² all interrupted axons had not degenerated until 7 days. Following degeneration, granular debris derived from disintegrated axonal organelles can be found surrounded by Schwann cell processes. Although most of this debris is cleared earlier, some may persist for up to 15 days.⁸² In the wake of axon degeneration, clusters of finger-like or curvilinear Schwann processes form within the confines of the basal lamina. These clusters, which contain few or, more often, no axon profiles, form as early as 2 to 3 days after injury.⁸¹ By 15 days with complete clearance of the degenerated axon debris, the Schwann cell processes are more compactly arranged. Schwann cell processes are attenuated to form plate-like or layered arrangements or ramified spidery profiles. The removal of axonal debris is effected by both Schwann cells and macrophages.⁸²

Regenerating axon sprouts have been identified as early as 5 or 6 days after experimental injuries as they traverse the gap between the severed or crushed ends of the nerve.^{80,81} The regenerating axons are notably smaller and more abundant than the originals; thus the axon to Schwann cell ratio is increased.^{80,81} The regenerating sprouts are encompassed

and guided by the surviving basal lamina; initially they are not closely related to the Schwann cell processes. Observations 2 months after nerve interruption reveal a decline in the numbers of regenerated axons, and the survivors re-establish more or less normal relationships with the Schwann cell processes.⁸¹ By 6 months, further reduction of sprouts restores the number of axons per Schwann cell unit to normal levels.⁸³

In spontaneous neuropathies resulting in substantial degeneration of unmyelinated fibers, the loss is indicated by various histopathological sequelae. Fiber loss is most distinctly indicated by increased numbers of Schwann cell subunits that are devoid of axons.⁸⁴ These empty Schwann cell profiles can be distinguished from the Büngner's bands that form as myelinated fibers degenerate. The latter differ in that they have larger diameters, more irregular shapes, and folded basal laminae, and often they contain telltale myelin debris or pi granules.^{84,85} The increase in empty Schwann cell profiles or subunits is due to loss of unmyelinated axons as well as Schwann cell proliferation. Regeneration of unmyelinated axons, as in the case of experimental nerve interruption, is indicated by increased numbers of small unmyelinated fibers. Increased numbers of **collagen pockets** also have been found in Schwann cell subunits after unmyelinated axon degeneration.^{84,86} The increase in these pockets may occur as the spaces vacated by degenerated axons are filled by longitudinally arranged collagenous fibrils.⁸⁶

Distal axonopathy

The term **distal axonopathy** is now applied to diverse disorders that produce degeneration of the terminal and preterminal axon. These include nutritional deficiencies, intoxications, metabolic disorders, and inherited diseases. Previously, degenerations of the distal axon had been identified as "dying back" of the axon. Cavanagh⁸⁷ identified "dying back" neuropathies as those in which coincidental degeneration of axon and myelin occurred more prominently in distal than in proximal nerves. The longest nerve fibers were most vulnerable, and they were damaged distally. The axon degeneration then appeared to progress in retrograde or centripetal fashion toward the cell body.⁸⁸ It had seemed that chromatolysis developed late when the degenerative process drew close to the cell body, yet with some toxins dispersion of Nissl appeared as an early chromatolysis-like change.^{89,90} Maintenance of a very long axon with great areas of membrane and no local synthetic ability is a large logistical problem for the neuron. Under equilibrium conditions, maintenance is possible, but when there is deprivation of energy, antioxidant substance deprivation, or physical obstruction of axon transport, the more remote portions of the axon degenerate.^{88,91} Proffered examples of dying-back neuropathies have included organophosphate intoxication, thiamine deficiency, vitamin E deficiency, isoniazid intoxication, amyotrophic lateral sclerosis, and Werdnig-

Hoffman disease. Further study of organophosphorus neuropathy, however, revealed that axon degeneration initially was focal and not actually terminal, but the degeneration soon spread in a somatofugal direction to involve the entire axon distal to the initial focus.⁹² In the case of primary sensory neurons, distal axonopathies are characterized by terminal degeneration both of the central axonal projection in the spinal dorsal columns and of the peripheral axon. This bipolar degeneration of sensory neurons has been called **central-peripheral distal axonopathy**. Acrylamide intoxication, for example, produces a central-peripheral distal axonopathy in which neurofilaments first accumulate paranodally in the distal portions of the largest and longest axons.⁹³ Because fast axonal transport provides for the structural and metabolic maintenance of the nerve terminal, its impairment has been suspected to be of primary importance in the pathogenesis of distal axonopathy.^{94,95} Other investigators have suggested that distal axonopathy reflects defective retrograde axonal transport.⁹⁶ Brimijoin⁹⁷ has pointed out that many newly synthesized proteins are rapidly transported to the distal axon, where they eventually undergo a process of "turnaround" and are conveyed back to the perikaryon for degradation. Using a pulse-labeling technique to study axonal transport, he concluded that some toxin-induced distal axonopathies result from impaired "turn-around," which results in organelle accumulation and swelling in the terminal and preterminal axon.

Clearly, the pathogenic factors operating in the various distal axonopathies are complex. The feature common to all would seem to be impaired transport within the distal axon.⁹⁵

Segmental demyelination and its consequences

Segmental loss of myelin around intact axons occurs as a pathological change in both inherited and acquired diseases of the peripheral nerves. At the light microscopic level, this change and its prevalence can be best appreciated on teased nerve samples. Gombault⁹⁸ first employed osmicated teased preparations of guinea pig peripheral nerve to distinguish the demyelinating effects of chronic lead administration from the changes of Wallerian degeneration. Many of his illustrations of isolated axons actually depicted the repair process through which segments were remyelinated following myelin degeneration. The remyelinated segments, which are now called **intercalated internodes**, were invariably shorter than the undamaged originals, and correspondingly the restored myelin was thinner and thus less osmiophilic.

Segmental loss of myelin commonly occurs as a primary change as a result of damage to the Schwann cell or damage to the myelin per se. It has been demonstrated that segmental demyelination also may occur secondary to chronic neuronal abnormalities that lead to axonal atrophy.

The longitudinal extent of myelin degeneration varies from relatively short paranodal loss of ensheathment to segmental involvement of one or even multiple consecutive

internodes. The classic and most studied examples of primary segmental demyelination include those induced by toxins, such as lead and diphtheria, as well as those that have an immune basis, such as experimental allergic neuritis (EAN).⁹⁹

The specific mechanism by which lead brings about demyelination is a matter that has not been fully resolved, although many suspect that damage to the Schwann cells is of prime importance.^{96,100,101} Similarly, the metabolic effects of diphtheria toxin that bring about demyelination after a relatively long latent period are not fully explained,¹⁰² although failure of myelin synthesis to keep pace with turnover of sheath constituents has been considered.¹⁰³ Definition of the demyelinating process in EAN is complicated by differences in the inciting antigens as well as by variations in the responses of different species. In early ultrastructural studies of EAN in the rat, Lampert¹⁰⁴ observed that demyelination began when infiltrating mononuclear cells came in direct contact with the sheaths. This contact produced focal dissolution of the lamellae that preceded invasion by macrophages that then stripped the damaged myelin from the axon. In all the segmentally demyelinating diseases, loss of myelin usually begins adjacent to the nodes of Ranvier. In EAN in the rabbit, the disruption of paranodal myelin is associated with the presence of macrophages¹⁰⁵; however, in the guinea pig, the demyelinating changes were similar to those induced by diphtheria toxin in that they also appeared at the nodes and without direct involvement of mononuclear cells.¹⁰⁶ A number of recent studies of EAN suggest that serum factors may initiate myelin damage in advance of mononuclear cell contacts.¹⁰⁷

In secondary demyelination as observed in human uremic neuropathy,¹⁰⁸ in Friedreich's ataxia,¹⁰⁹ and as a result of permanent axotomy,¹¹⁰ the loss of myelin is a consequence of axonal atrophy. Secondary demyelination has been distinguished by the following structural characteristics: (1) myelin wrinkling of original internodes, (2) axonal diameters disproportionately small for the thickness of the myelin sheaths, (3) longitudinal clustering of demyelinating or remyelinating segments along isolated axon lengths, and (4) substantial amounts of axon loss in the presence of segmental demyelination.¹¹⁰ The degenerative changes have been charted in the following chronology: axonal atrophy → paranodal and internodal demyelination → remyelination → further axon atrophy → axonal degeneration.

Recurrent segmental demyelination with its attendant proliferation of Schwann cells leads to the formation of **onion bulb** configurations (Fig. 7-12).^{106,111,112} These structures consist of concentric arrays of Schwann cell processes arranged somewhat like the rings of a transected onion around a central axon. The axon may appear to be demyelinating, demyelinated, or remyelinating. When multilamellate onion bulbs form and persist in large numbers, in aggregate they can lead to grossly discernible enlargement of cranial and peripheral nerves. Such palpable enlargement

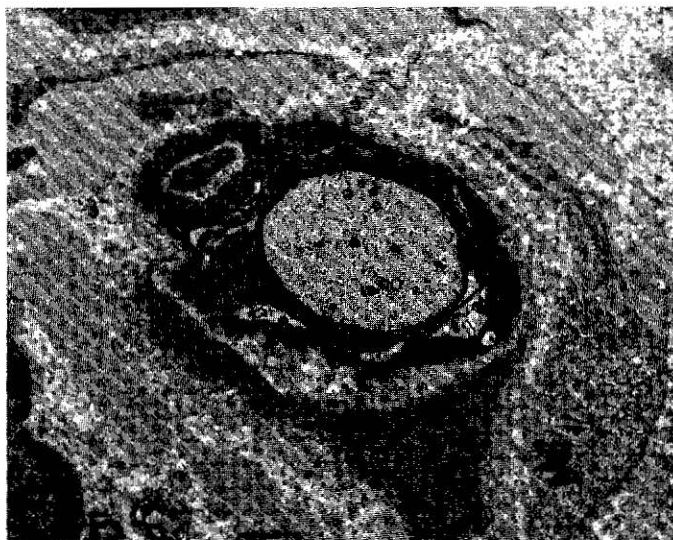


Fig. 7-12. Onion bulb, dog. Schwann cells proliferate about the central thinly myelinated axon. Endoneurial collagen is increased. ($\times 8750$.)

is characteristic of **hypertrophic neuropathy**. In hypertrophic neuropathy, the nerve enlargement commonly is attributable not only to onion bulb formation but also to endoneurial collagenous fibrillogenesis and perhaps to intrafascicular accumulations of Renaut body-like mucoid tissue as well.¹¹³

Onion bulb formation begins with partial or total internodal demyelination, which is followed by mitotic division of Schwann cells. This proliferation yields Schwann cells in excess of those that become applied to the denuded axon lengths and take part in remyelination. These supernumerary, non-myelinating Schwann cells are displaced peripherally, and the numbers of these satellites grow centrifugally with recurring bouts of demyelination.

In addition to the aforementioned demyelinating conditions that have been produced in laboratory species, there are spontaneous demyelinating diseases of peripheral nerves in domestic animals. For example, an inherited Schwann cell defect in Tibetan Mastiff dogs¹¹⁴ results in primary segmental demyelination, remyelination, and formation of onion bulbs. Examples of acquired demyelinating disorders also can be cited. In acute polyradiculoneuritis of dogs, there is usually extensive evidence of primary demyelination.¹¹⁵

In the few reported cases of canine and feline chronic polyradiculoneuritis,¹¹⁶⁻¹¹⁸ recurrent demyelination has resulted in onion bulb formation. In these examples of inherited and acquired primary segmental demyelination, variable amounts of axonal degeneration also have been found. In the horse, secondary segmental myelin loss appears to occur in response to distal axon degeneration in the recurrent laryngeal nerves in laryngeal hemiplegia.¹¹⁹ In keeping with the usual asymmetric clinical deficit, the distal axonal and more proximal myelin changes are more prominent on the

left. Additional examples of primary and secondary demyelinating diseases are presented later in this chapter.

References are on page 485.

COMMON ARTIFACTS IN THE PERIPHERAL NERVOUS SYSTEM

Some artifacts encountered in the peripheral nervous system are related to the process of **fixation**. More specifically, the influencing factors include (1) the manner in which the nerve sample is removed, (2) the method by which the specimen is immersed in the fixative, and (3) the type of fixative used.

In obtaining peripheral nerve samples by biopsy or at necropsy, the ends of the unfixed samples are easily compressed by forceps or the cutting instruments used in the resection. The resulting crush artifact commonly appears on longitudinal paraffin sections as an area of axon swelling at ends of the samples. It is also important to recognize the distorting effects of seemingly slight compression caused by transection or mincing of unfixed nerve with a scalpel or razor blade.^{1,2} On cross-section, it can be seen that this compression causes displacement of the myelin sheath from the surface of the axons, which may become distended by displaced neurofilaments. In these crush-distorted fibers, the axolemma may be invaginated into the axoplasm, and this may result in irregular partitioning or subdivision of the axon.³

With slippage and displacement, the myelin is telescoped in adjoining areas to form irregular thickenings of the sheath. In the areas of thickening, the redundant myelin may fold to form incursions into the axon or produce evaginations into the Schwann cell. Even in the paranodal areas of large fibers that have not been compressed, myelin folds may produce evaginations into the Schwann cell or invaginations into the axoplasm. On transverse sections, the continuity of these projections with the sheath may not be visualized, and they then simulate the appearance of myelin ovoids.^{4,5} It is important that these alterations that result from slippage and telescopic thickening of the myelin be recognized as artifacts and not be misinterpreted as demyelination on one hand or hypermyelination on the other.^{2,6} As compressive changes seem to be limited to within 2 mm of the cut end, these can be avoided by discarding at least 2 mm from the ends of the sample after fixation.⁶

When nerve samples are resected, it is common practice to tense these specimens before they undergo immersion fixation. The specimen can be tensed in the container of fixative by tying one end of the resected length to the container lid and fixing a light weight (e.g., split shot or a hardware nut) to a suture that has been placed in the epineurium at the other end. When sampling many nerves at necropsy, it is much easier and faster to stretch out the nerve lengths on tongue depressor blades, where they will remain adhered after immersion in the fixative.

In peripheral nerves that have not been fixed under ten-

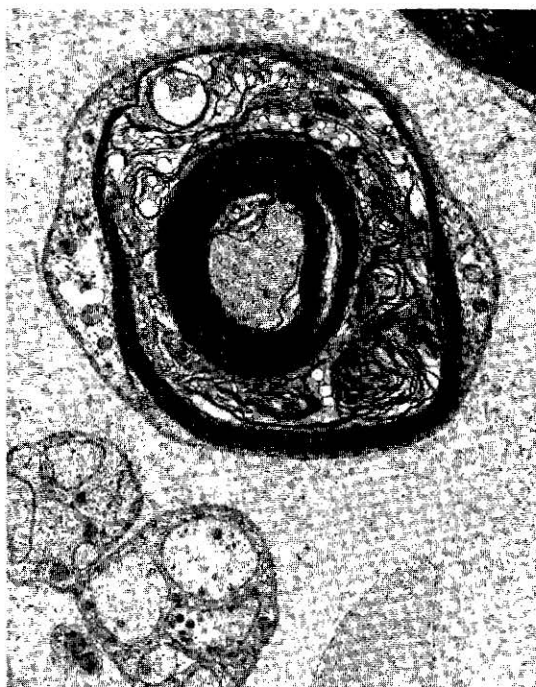


Fig. 7-13. Myelin artifact. Femoral nerve, dog. Distension of the Schmidt-Lantermann cleft due to vesicular transformation of the myelin sheath. ($\times 12,800$.)

sion and are sectioned longitudinally, it is common to observe that the axons in aggregate pursue an undulating or zigzag course. This is not an artifact, as is commonly suspected. Rather, it is present *in vivo* as an adaptation that provides slack and allows peripheral nerves to withstand moderate stretching without damage.⁷ It is the zigzag course of the axons that through an optical effect creates the macroscopic appearance of spiral bands along peripheral nerves. These, the so-called **spiral bands of Fontana**, can be seen on unfixed, unstained nerve trunks with the naked eye or more distinctly with a hand lens.⁸ When the nerve is tensed, the axons straighten, and concomitantly the bands disappear. Neither the undulating axons nor the bands are found in the cranial nerves or spinal roots.

As in other tissues, delays in fixation bring about post-mortem distortions in myelinated axons, especially the larger ones. Hirano² has identified swelling of the cytoplasmic areas of the myelin sheath as an obvious change induced by fixation delay. This swelling is often obvious in the inner loop and at the Schmidt-Lantermann incisures. In

the latter location, the swelling produces wide separations within the sheath (Fig. 7-13). Distension of the inner loop of the myelin sheath can be marked and cause distortion of the axon. These artifactual swellings may be difficult to distinguish from the focal myelin ballooning that has been described as an age-related change in a number of species.⁹

Another myelin change associated with delayed fixation seems to have been confused in the past with an *in vivo* form of demyelination. Some of the earlier ultrastructural studies on the lesions of acute idiopathic polyradiculoneuritis reported vesicular dissolution of myelin as a form of myelin breakdown that occurred in the absence of cellular invasion. A more recent study indicates myelin vesiculation occurs as a postmortem artifact in any nerve samples obtained 24 hours after death.¹⁰

Additional artifacts may be induced by the fixative *per se* or subsequent tissue processing. For example, when osmium tetroxide was used as a primary fixative for EM, its poor penetration resulted in lack of fixation in the interior of larger tissue blocks. A similar problem occurs in larger blocks of nerve when osmium is used in post-fixation. As a result, the myelin sheaths of the internally situated nerve fibers are not stained by reduced osmium and appear en masse as a pale area on semithin sections. Osmium as a primary fixative also did not permit ultrastructural visualization of neurotubules. The use of glutaraldehyde in contemporary fixative solutions, however, ensures microtubule preservation.¹¹

In formalin-fixed tissue processed according to the paraffin technique, other artifacts are present. Primary fixation in an alcohol solution or dehydration of a formalin-fixed nerve in ethanol prior to paraffin embedding can result in tissue shrinkage and separation artifacts. These may appear as a widened subperineurial space that highlights the periphery of the nerve fascicle or as widened clefts in the endoneurium. In spinal ganglia, the space develops between the retracted neuronal cell body and the satellite cells.

The use of solvents—that is, alcohol and xylene—in paraffin processing results in extraction of much of the lipid of the myelin sheaths. As a result, a largely proteinaceous residue of the sheath presents with a foamy or vacuolated appearance when stained with luxol fast blue, aniline blue, and eosin, among others. This artifactual residue, the **neurokeratin network**, may present a radial pattern when seen on cross-section.

References are on page 487.

Inflammatory diseases of the peripheral nervous system

ACUTE IDIOPATHIC POLYRADICULONEURITIS

In North America, the most common form of acute polyradiculoneuritis in animals is **coonhound paralysis (CHP)**. This syndrome was first described by Kingma and Catcott¹ as an acute ascending paralysis that appeared in dogs 7 to 10 days after they have been bitten or scratched by a raccoon. Although Kingma and Catcott confirmed that in 14 of 16 affected hounds, encounters with raccoons had been witnessed, other causal associations, including spinal trauma,² toxin ingestion,³ and botulism,⁴ were proffered.

Typically, weakness develops in the hind limbs and ascends rapidly, resulting in a flaccid symmetric tetraplegia or paresis. Occasionally weakness appears first in the forelimbs and descends. CHP is largely an occupational hazard for raccoon-hunting hounds (e.g., Walker, Black and Tan, Blue Tick, and Redbone Hounds), but other dogs that have chance encounters with raccoons may also be affected. The veterinarian is usually presented with a quadriparetic dog that may bear scars about the head from a recent battle with a raccoon. Paralysis usually peaks within 10 days of onset. In some dogs a progression to tetraplegia is very rapid, and in these animals impending respiratory paralysis may be signaled by labored respiration 72 to 96 hours after the onset. Severely affected dogs rapidly become tetraplegic and are flexic in the extremities and are unable to lift their heads or wag their tails. The voice is usually lost or greatly weakened, and occasionally there may be facial weakness. Evidence of other cranial nerve involvement (e.g., dysphagia or ophthalmoplegia) has not been observed. In fact, paralyzed dogs usually maintain an appetite and eat and drink eagerly when assistance is provided. Although motor deficits are invariably more marked than sensory changes, many animals seem to experience considerable discomfort on light palpation on the extremities. In tetraplegic animals, muscle atrophy develops quickly.

Electrodiagnostic testing commonly provides widespread evidence of motor denervation. Fibrillations and positive-sharp waves are recorded frequently, and myotonic bursts occur occasionally. Studies of motor nerve conduction velocities have disclosed variations among animals and among nerves in the same animal. In some dogs normal values have been obtained, in others velocities have been moderately or markedly delayed, and in some instances supramaximal stimulation of nerves failed to evoke a recordable muscle response. Although CSF samples from the cerebello-medullary cistern usually have normal cell and protein levels, occasional samples contain slightly elevated protein. Greater protein elevation is demonstrated as part of an albuminocytological dissociation in samples taken by lumbar

puncture.^{5,6} Because the lesions in CHP concentrate proximally in the ventral or motor roots, sensory nerve biopsies usually contain little evidence of any deviation from normal.

Although some paralyzed dogs succumb to respiratory failure or intercurrent illness, recovery is usual. The speed and completeness of recovery vary considerably. Dogs with rapidly developing, generalized muscle wasting and dense denervation potentials on electromyography can be expected to have delayed recoveries that may be marred by some residual weakness. These same animals are at risk to develop severe decubital ulcers.

Coonhound paralysis is rare. Many hounds are bitten by raccoons, yet few develop this paralysis. Dogs that have recovered from CHP are not immune to future attacks. Study of many case histories indicates that certain hounds are susceptible, and individuals that have sustained one bout of CHP are prone to redevelop the paralysis on subsequent encounters with raccoons.^{5,7,8} Some hounds have sustained five and six discrete attacks of CHP, and each has been preceded by an encounter with a raccoon.

Although the cause remains unknown, one severe bout of CHP was produced experimentally by injecting 1 ml of a pooled sample of raccoon saliva into a Walker Hound. This dog, after recovering from two natural attacks of CHP, had been held in a viral isolation facility for 1 year prior to the saliva injection.⁹ Many additional attempts to produce CHP by injections of raccoon saliva have failed. There has been some suggestion that not all raccoons are capable of inducing CHP, even in dogs judged susceptible by virtue of prior attacks. Thus far, attempts to isolate a virus from offending raccoons or paralyzed dogs have been unsuccessful.

Recent ELISA assays using pooled raccoon saliva at 1:2000 dilutions as an antigen have demonstrated circulating antibodies in moderate to strong reactions in dogs with CHP.⁶ Sera from normal dogs or dogs with unrelated neurological disorders have not reacted similarly. It is interesting that sera of dogs that had recovered from bouts of CHP continued to react with raccoon saliva. This suggests that persistent sensitivity may be a factor in recurrence of this paralysis.

Pathological changes are usually entirely microscopic and are most marked in the ventral roots and spinal nerves and taper off in the peripheral nerves. Dorsal root involvement varies but usually is minor. Changes consist of leukocytic infiltration of widely varying intensity and composition, paranodal and segmental demyelination (Fig. 7-14), as well as concomitant degeneration of axons and myelin. Venous congestion with prominent leukocytic cuffing occurs in the

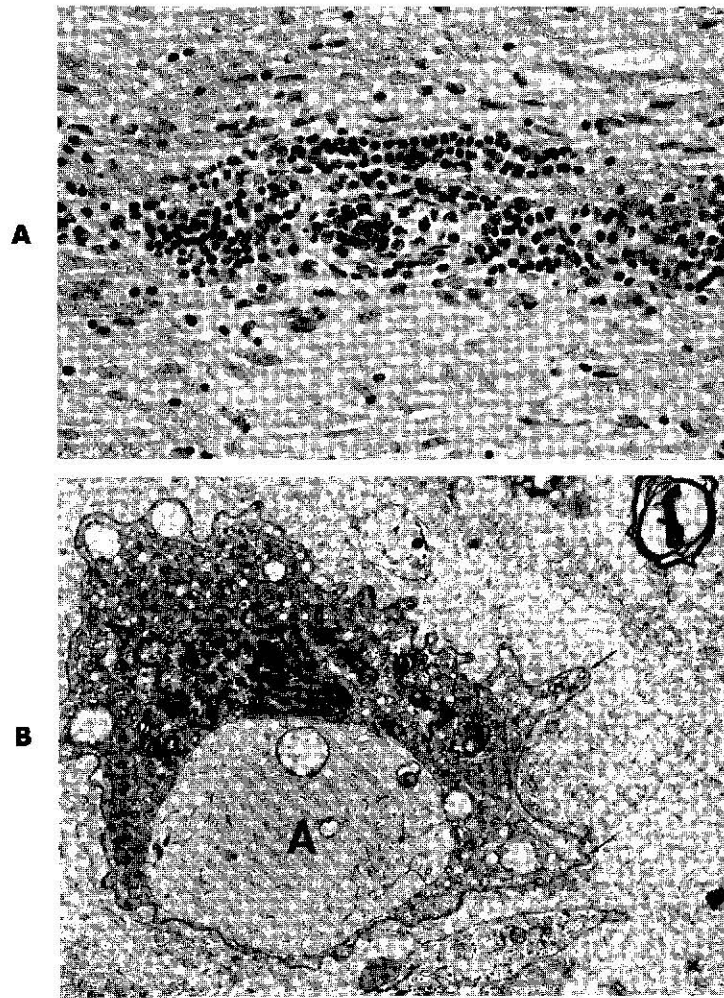


Fig. 7-14. Acute idiopathic polyradiculoneuritis, dog. **A**, Perivenular lymphocytic influx, lumbar-sacral root. (H&E, $\times 140$.) **B**, Macrophage within Schwann cell basal lamina (arrows) abuts demyelinated axon (A). ($\times 7600$.)

roots and nerves in some dogs, yet in others there is no discernible congestion, and cellular infiltrates are much more diffuse.

The severity of demyelination and axon degeneration varies, as do the intensity and composition of the inflammatory infiltration. In severely affected dogs dying soon after the onset with respiratory paralysis, the infiltrates may be sparse and contain neutrophils as well as mononuclear cells; in dogs with longer survivals, the infiltrates consist of lymphocytes, plasma cells, and macrophages.

Demyelination, as demonstrated on teased nerve preparations, ranges from slight paranodal loss to extensive loss over consecutive internodes. Electron microscopic studies indicate that mononuclear cell contact or invasion is not essential for the initiation of myelin breakdown.⁵ Advanced degenerative changes in the myelin sheaths (e.g., swelling and vesiculation) are observed in the absence of proximate mononuclear cells or macrophages. Macrophages often ap-

pear within degenerating myelin sheaths and between the degenerating sheath and the axon (Fig. 7-14, *B*), but in these situations they seem to be responding to disintegration of the myelin rather than causing it. Demyelination is accompanied by a reduction in axon diameter. Schwann cell proliferation and remyelination ensue rapidly. Remyelinating segments are marked by intercalated internodes, which are notably thinner and shorter than the originals.

The prevalence of axon degeneration varies. It has been very prominent in dogs dying of acute respiratory paralysis and also abundant in dogs with prolonged paralysis and muscle atrophy. In such cases, central chromatolysis may be found in somatic motor neurons of the spinal cord.

Regenerative changes follow rapidly in the wake of axon degeneration. Cords of proliferated Schwann cells (i.e., B ngner's bands) mark the sites of earlier axon loss, and in the spinal roots these appear to be quickly invaded by multiple regenerating axon sprouts. It would seem that rel-

atively few sprouts establish contact with denervated muscle, and many show signs of degeneration.

Coonhound paralysis has been compared with acute idiopathic polyradiculoneuritis in humans—**Guillain-Barré syndrome** (GBS).^{5,7,10} Both are manifest clinically as acute ascending paralysis and characterized pathologically by inflammatory infiltration, demyelination, and variable amounts of axon degeneration in spinal roots and peripheral nerves.¹¹ In CHP an encounter with a raccoon has been a consistent antecedent, whereas in GBS antecedents often have not been discerned or have consisted of diverse viral illnesses, *Campylobacter jejuni* infections, vaccinations, surgery, and the like.¹¹ Despite their diversity, it is believed that the antecedents have a common ability to trigger autoimmune demyelinating polyradiculoneuritis. Some evidence suggests that GBS may be initiated by cell-mediated mechanisms and accentuated by humoral factors,¹² but precise definition of the autoantigen and the pathogenetic process is lacking.¹³

Despite the clinical similarities between GBS and CHP, there seems to be some divergence in the pathological findings. In many cases of CHP, the leukocytic infiltrates have been sparse relative to those commonly depicted in cases of GBS.¹⁴ The seemingly obligatory role of macrophages that has been described in many ultrastructural studies of the demyelinating process in GBS¹⁵⁻²¹ has not been found in CHP, where these cells appear to respond to myelin degeneration rather than initiate it. The myelin lesions in CHP more closely resemble those induced by antibody contained in locally transferred GBS or experimental allergic neuritis sera.⁵ Recent studies of experimental allergic neuritis, a rodent model for GBS, have revealed that myelin vesiculation precedes macrophage stripping, an additional indication that serum factors may play a role in demyelination.²² In this regard, there is now evidence that IgM antibody from GBS patients binds to peripheral nerve myelin and participates in demyelination through complement activation.²³ It has been suggested that in GBS, serum-induced demyelination results from two processes: acute demyelination occurring in the absence of contact with inflammatory cells and delayed demyelination mediated by host macrophages.²⁴ This and similar hypotheses suggesting variation among cases of GBS in the relative demyelinating impacts of antibody and cell infiltrates afford an explanation for the wide ranges found in the density of inflammatory infiltrates in recent pathological studies of nerves from GBS patients.²⁵⁻²⁷

In CHP, axon degeneration has been a usual and sometimes prominent finding, whereas in GBS axon involvement has been usually reported as minimal. Widespread degeneration of myelinated and unmyelinated fibers has occurred however, exclusive of segmental demyelination in a rarer acute axonal form of GBS.²⁸⁻³⁰ Feasby and colleagues²⁹ note that axonal degeneration in GBS can occur in two ways: as a consequence of demyelination and inflammation or as a

primary event without inflammation or demyelination. Thus, there appear to be dissimilarities in the lesions of CHP and those in the usual form of GBS. It is not clear, however, with the reported range in lesions among GBS patients if CHP has pathogenetic mechanisms in common with some cases of the human disorder.

Although coonhound paralysis is easily identified because of its unique antecedent, it is not the only canine form of acute polyradiculoneuritis. Vandeveld and associates³¹ described an acute inflammatory disease of the spinal roots in four dogs in Switzerland with no possible access to raccoons. Two of the dogs developed tetraparesis or tetraplegia with hyporeflexia or areflexia and preserved pain sensation. No antecedent was identified in three of the dogs; however, the fourth, a severely paralyzed Cocker Spaniel, had been recently immunized against rabies with an inactivated vaccine prepared from a suspension of newborn mouse brain. Pathological changes were the same in the spinal roots of all four dogs. Perivascular and interstitial infiltrates of lymphocytes, monocytes, and macrophages took part in segmental demyelination. Axon interruption in the ventral roots also led to retrograde chromatolysis in the ventral horns of the spinal cord. It was concluded that the pathological changes—diffuse mononuclear cell infiltrates in spinal roots with segmental demyelination and lesser amounts of axon degeneration—were identical to those of CHP.

Northington and co-workers³² described **acute idiopathic polyneuropathy** in 10 dogs with no exposure to raccoons or toxins. Progressive weakness and hyporeflexia developed over 1 to 21 days. Electrical studies detected muscle denervation potentials, and nerve conduction delays were found in some cases. Nerve biopsies were described as normal, mildly abnormal, or with axon degeneration. It was concluded that this was a demyelinating polyneuropathy in which mononuclear cells infiltrated the motor roots and nerves near their spinal origin.³³ Brown and colleagues³⁴ found that serum from five affected dogs demyelinated the injected nerves of recipient rats in the presence of complement more notably than did sera from control dogs. In addition to the group of dogs studied by Northington and Brown, additional case reports suggest that acute polyneuritis has varying clinical presentations.^{35,36}

These studies suggest that the term acute idiopathic polyradiculoneuritis should encompass more than CHP and that events other than a raccoon bite may precipitate inflammatory demyelinating disease in canine spinal roots.

There is a report of **acute idiopathic polyneuritis** in the **cat**,³⁷ wherein severe weakness evolved within 24 hours. Initially this 4-year-old, neutered female presented with fever, icterus, anemia, and tetraparesis. The fever quickly abated after administration of chloramphenicol; weakness persisted, however, and muscle atrophy became marked by 2 weeks after the onset, when the animal was euthanized. Microscopic study of multiple peripheral nerve samples re-

vealed extensive degeneration of myelinated nerve fibers and the presence of some lymphocytic and plasmacytic perivascular cuffs. Evidence of segmental demyelination was absent.

A brief report of **polyradiculoneuritis** in a 6-week-old male **goat** describes segmental demyelination, Schwann cell proliferation, and mononuclear cell infiltration in the spinal roots. These changes were compared with those in the Landry-Guillain-Barré syndrome.³⁸

Polyradiculoneuritis has also been described in exotic species, including a **bear**³⁹ and a **sea lion**.⁴⁰

References are on page 487.

CHRONIC POLYRADICULONEURITIS

The term chronic polyradiculoneuritis is not meant to imply a distinct nosological entity. Instead, the term is applied to rare, slowly progressive, or relapsing motor and sensory deficits that have been associated with inflammatory changes in the spinal roots and cranial and peripheral nerves. Neurological impairments with these general characteristics have been reported sporadically in mature dogs¹⁻⁵ and cats.⁶⁻⁸

Signs develop over a period of weeks or months, and temporary remissions occur spontaneously. Although corticosteroid therapy has produced sustained remission,^{6,8} this treatment is not invariably effective.¹ Initial limb weakness may be mild, asymmetric, or unilateral and so localized that it simulates an orthopedic problem. Weakness may be manifest as a gait abnormality, exercise intolerance, or a reduced ability to perform postural reactions. Signs of cranial nerve involvement (e.g., temporal muscle atrophy, dysphonia, facial weakness) may be observed also. Spinal reflex findings vary with the stage and distribution of the weakness, but with increasing chronicity reflexes often are sharply reduced or absent. Muscle wasting usually progresses with time, but it is not evident in all cases. Sensory findings in the limbs may include hyperesthesia, hypalgesia, and proprioceptive loss. Cerebrospinal fluid studies may reveal no abnormality, but an albuminocytological dissociation (i.e., elevated protein without concomitant leukocytosis) has been recorded in some dogs. Electrical studies usually reveal denervation potentials and delayed motor nerve conduction velocities. In some instances, supramaximal stimulation of peripheral nerves has failed to evoke a recordable muscle response.

In the reported cases of chronic polyradiculoneuritis, mononuclear cell infiltrates in the roots and nerves have been a consistent pathological finding. However, the intensity and distribution of these infiltrates and the proportions of lymphocytes, plasma cells, and macrophages have varied widely. For example, in one Labrador Retriever with chronic, progressive weakness and wasting, intense inflammatory infiltrates were found in the nerve sheaths—the epineurium and perineurium. In most cases, however, infiltrates have been prominent within the roots and nerves,

where they form perivenular, diffuse, or focal arrays. In some reports, the mononuclear infiltrates were clearly associated with active segmental demyelination.^{1,7} In these cases, macrophages were aligned along demyelinating or demyelinated axons, yet it was unclear whether these cells were responsible for initiating the demyelination or were secondarily involved. Axon degeneration, although usually overshadowed by demyelinating changes, may be extensive in some animals.^{4,5} In one dog with recurrent episodes of generalized weakness, repeated bouts of demyelination lead to widespread onion bulb formation in the cranial and peripheral nerves and roots, with little evidence of axon involvement. Large onion bulbs and expansive areas of mucoid degeneration within the endoneurium caused gross enlargement of the nerves. If present, central nervous changes usually occur secondary to peripheral disruption of axons.

In those cases in which the changes were largely demyelinating, the lesions closely resembled those described in human chronic inflammatory demyelinating polyradiculoneuropathy.⁹⁻¹¹ The pathological hallmarks of the latter include mononuclear cell infiltrates (often perivascular), segmental demyelination and remyelination, and, with greater chronicity, hypertrophic neuropathy. Axon degeneration may be surprisingly prevalent. As with the canine cases, there have been difficulties in humans in precisely delimiting the clinicopathological parameters of this neuritis.¹²⁻¹⁴

References are on page 488.

BRACHIAL PLEXUS NEURITIS

Brachial plexus neuritis (neuropathy) is a rare condition in domestic animals with very few published reports in the **dog**¹⁻⁴ and **cat**.⁵ Duncan and Griffiths⁶ have seen four dogs with bilateral brachial plexus lesions, but make only brief reference to them. Similarly, a retrospective study of bovine neurological disease includes brief mention of brachial plexus neuritis in a cow.⁷ This paralysis closely resembles human afflictions that have usually been subsumed under the heading of brachial plexus neuropathy.

In two of the reported canine cases, bouts of urticaria preceded the onset of forelimb weakness by several hours, and in one of these the reaction was associated with ingestion of horse meat. Two animals cried as if in pain shortly before the onset of forelimb weakness. Paralysis developed precipitously and reached a maximum soon after the onset. In one dog, weakness and subsequent wasting were confined to the shoulder muscles. In two others, the forelimb gait was more severely compromised. Neurological and electrodiagnostic testing revealed that involvement was bilateral and asymmetric and included shoulder, brachial, and antebrachial muscles. In one dog, an apparent loss of antebrachial sensation was confirmed on biopsy of the cutaneous branches of the radial nerve, which had large numbers of degenerated fibers. Recovery from weakness and muscle

wasting was protracted, and one dog was euthanized when there was no sign of remission after 7 weeks.

Histopathological studies in this dog revealed extensive axon degeneration bilaterally in nerves derived from the brachial plexus, such as the musculocutaneous, median, radial, and ulnar nerves. In accordance with the clinical and electrical findings, the peripheral nerve degeneration was asymmetric. For example, axon degeneration occurred in the suprascapular nerve on the left but not on the right. On the right, where all heads of the triceps muscle were severely wasted, approximately 90% of the axons in the radial nerve had been lost, but on the left where just the medial head of the triceps was atrophied, only about 30% of the radial nerve axons had degenerated.

Pathological changes appeared most proximally in the ventral branches of the spinal nerves that give rise to the brachial plexus. The extent of damage within the fascicles of these branches of the spinal nerve varied. The changes were consistently those that follow axon degeneration. These changes appeared to be advanced and chronologically similar. Usually sites of axon loss were marked proximally and distally by Büngner's bands. These bands were compact or slightly distended by small residual amounts of degenerated myelin or droplets of neutral lipid. A few fascicles in the branches of the C7 spinal nerve contained lightly myelinated sprouts of regenerating axons. The endoneurium contained increased collagen and large numbers of lipid-laden macrophages. Mast cells were common in affected fascicles. Retrograde chromatolysis occurred in the somatic motor neurons of the cervical spinal intumescence and in the sensory cell bodies of the associated spinal ganglia. Distally, the pattern of muscle wasting often indicated a selective form of neural involvement. For example, examination of the right biceps and brachialis (two muscles innervated by the musculocutaneous nerve) indicated that the former was totally denervated while the latter was fully intact. In human brachial plexus neuropathy, this highly preferential, virtually all-or-none type of neurogenic muscle atrophy had been thought to reflect a very distal lesion of the axon or perhaps of the muscle itself.⁸

The clinical neurological findings in affected dogs are remarkably similar to those reported in human brachial plexus neuropathy. The latter has been observed in three forms: (1) a cryptogenic or idiopathic form that may have an identified antecedent, such as illness, trauma, surgery, or inoculation; (2) a serogenetic form that is now largely of historical interest because it followed treatments with heterologous antisera; and (3) an inherited form in which there is a familial predisposition to recurrent episodes of paralysis, some of which may be associated with pregnancy, a preceding illness, or strenuous use of the limb.^{9,10} An immunological pathogenetic mechanism has been suspected to underlie all three forms of this neuropathy. Opportunities to study the pathological changes in this nonfatal human disease have been very limited.¹⁰⁻¹² To date, there has been

a lack of unanimity regarding both the site and the nature of the lesions. To what extent the pathological findings in this canine paralysis are applicable to the human neuropathy is a matter for speculation. Surely the long time to recovery (6 months to 2 years) in most human patients is consistent with regrowth of axons that had been interrupted at proximal levels. The close temporal association between bouts of urticaria in the dogs and the onset of neurological impairment suggests that the latter may be part of an immediate hypersensitivity reaction that impacts proximally at the level of the spinal nerves. It is conceivable that amine-induced increases in vascular permeability with ensuing intraneural edema bring about the observed axon degeneration. The role of regional predispositions (e.g., bony confines, mast cell densities, and defects in the blood-nerve barrier) remains to be defined.

References are on page 488.

CANINE GANGLIORADICULITIS (SENSORY NEUROPATHY)

Nonsuppurative inflammation of cranial and spinal ganglia and roots has been a common finding, along with meningoencephalitis, in certain viral infections such as rabies, canine herpes viral infection, and pseudorabies. More recently, subacute idiopathic ganglioradiculoneuritis has been described in dogs without concurrent CNS involvement.¹⁻³ Clinical and pathological findings in the cases reported have been sufficiently similar to suggest a single nosological entity. Some of the cases of sensory neuronopathy recorded by Braund⁴ may also belong in this category.

Mature dogs of both sexes and various breeds present with deficits that appear rather abruptly but then progress over 1 to several months. Clinical findings, some which may be asymmetric, include ataxia, hypermetria, basewide stance, diminished postural reactions, depression or loss of tendon reflexes, facial hypalgesia, difficulty in prehending food, dysphagia, and masticatory muscle wasting. Megaeophagus, dysphonia, and self-inflicted injuries presumably in response to dysesthesias may also be observed. Cerebrospinal fluid findings range from normal to increases in both cells and protein. Adrenocorticoid treatment has not been effective; rather, it has been associated with rapid intensification.

At necropsy, the dorsal roots may appear discolored. Gross evidence of the ganglioradiculitis is sometimes evident as a whitish, V-shaped zone in the dorsal columns of the spinal cord (Fig. 7-15, A), reflecting the degeneration secondary to the ganglion injury. Microscopic study reveals nonsuppurative inflammatory changes that concentrate in the spinal ganglia and dorsal roots and the ganglia of the cranial nerves (Fig. 7-15, B and C). Similar changes are very infrequent in the motor roots and peripheral nerves. Infiltrates contain lymphocytes, macrophages, and plasma cells. Leukocytes occur in perivenular, perineuronal, and focal and diffuse interstitial arrays. In many ganglia, neu-

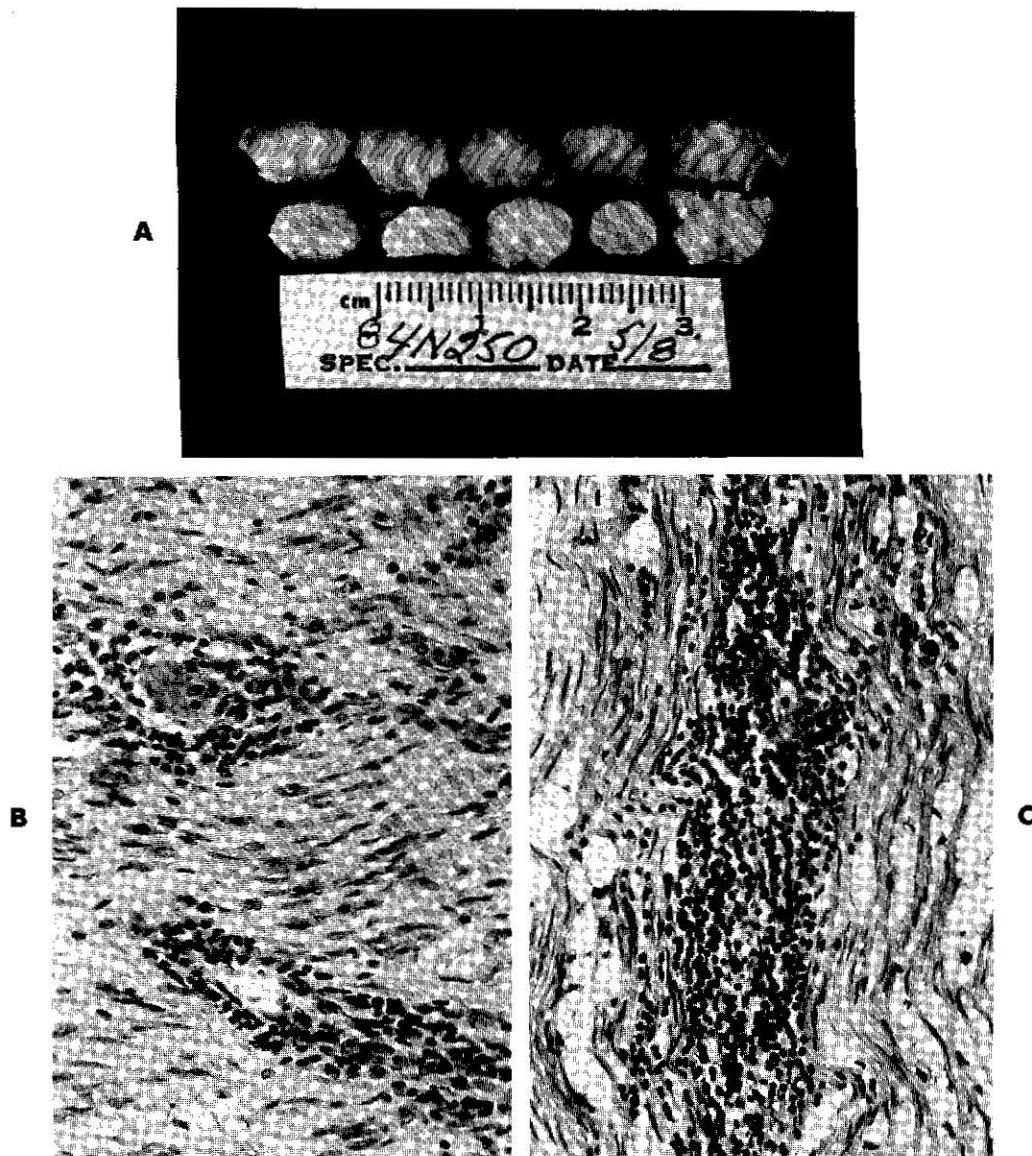


Fig. 7-15. Canine ganglioradiculitis. **A**, Wallerian degeneration and subsequent sclerosis in the spinal dorsal funiculus secondary to sensory neuron loss in ganglioradiculitis is evident as a V-shaped white area in the dorsal funiculus. **B**, Neuronophagia and cuffing, lumbar spinal ganglion. (H&E, $\times 350$.) **C**, Lymphocytic radiculitis and Wallerian degeneration. (H&E, $\times 350$.)

ronal degeneration is widespread. Sites of cell body loss are marked by Nageotte nodules (clusters of proliferated satellite cells). Many persisting cell bodies are shrunken and hyperchromatic. The satellite cells around such degenerating or necrotic neurons are often heavily infiltrated by mononuclear cells. Vacuolated and chromatolytic neurons also occur but less frequently. Leukocytic infiltrates in the dorsal roots do not extend into the spinal cord, but the neuronal destruction in the ganglia and roots is reflected centrally in Wallerian degeneration in the spinal dorsal columns. Similarly, neuron death in cranial nerve ganglia results in substantial degeneration in the brain stem in the spinal tract of the trigeminal nerve and the solitary tract. It is thought that the masticatory muscle atrophy may be caused by inflammatory involvement of motor root fibers as they course through the trigeminal ganglion. Inflammatory infiltrates have also been observed in sympathetic ganglia and in ganglia of the myenteric plexus.

Electron microscopic studies reveal degenerative changes in many ganglionic neurons including dilation of the endoplasmic reticulum, ribosome dispersion, and mitochondrial swelling. More severely affected neurons are shrunken. Such cells contain pyknotic nuclei and dark cytoplasm with heavily condensed arrays of neurofilaments and tubules. The satellite cells around these neurons are also affected. Some contain distended profiles of endoplasmic reticulum and swollen mitochondria. Often, satellite cells are abutted by perineuronal lymphocytes and macrophages. These mononuclear cells invade the encapsulating satellite cells and displace them from the sensory neuron surface (Fig. 7-16). In this way, macrophages and lymphocytes directly abut the plasma membrane of degenerating cell bodies. It may be that the invading leukocytes inflict neuronal and satellite cell damage, although degenerative neuronal changes occur in the absence of perineuronal leukocytes. Vascular changes may also be present. Endothelial hypertrophy and medial necrosis have been seen in ganglionic arterioles with adventitial leukocytic infiltrates.

The dorsal roots contain many B ngner's bands that formed in the wake of myelinated axon degeneration. Smaller, irregular clusters of flattened Schwann cell processes without axons suggest considerable loss of unmyelinated fibers as well. In keeping with the unrelenting clinical course and the observed loss of cell bodies, there is little evidence of axon regeneration or myelin loss independent of axon degeneration.

The cause of this canine sensory ganglionic radiculitis is unknown. To date, Siberian Huskies seem to have been over-represented among affected dogs,⁵ but the total number of reported cases is small, and it seems premature to ascribe a breed predisposition to this observation. A recent attempt to isolate virus from the spinal ganglia of an affected dog that was pretreated with adrenocorticoids was unsuccessful. In humans, strikingly similar ganglionic radiculitis may occur along with CNS changes in association with carcinoma,

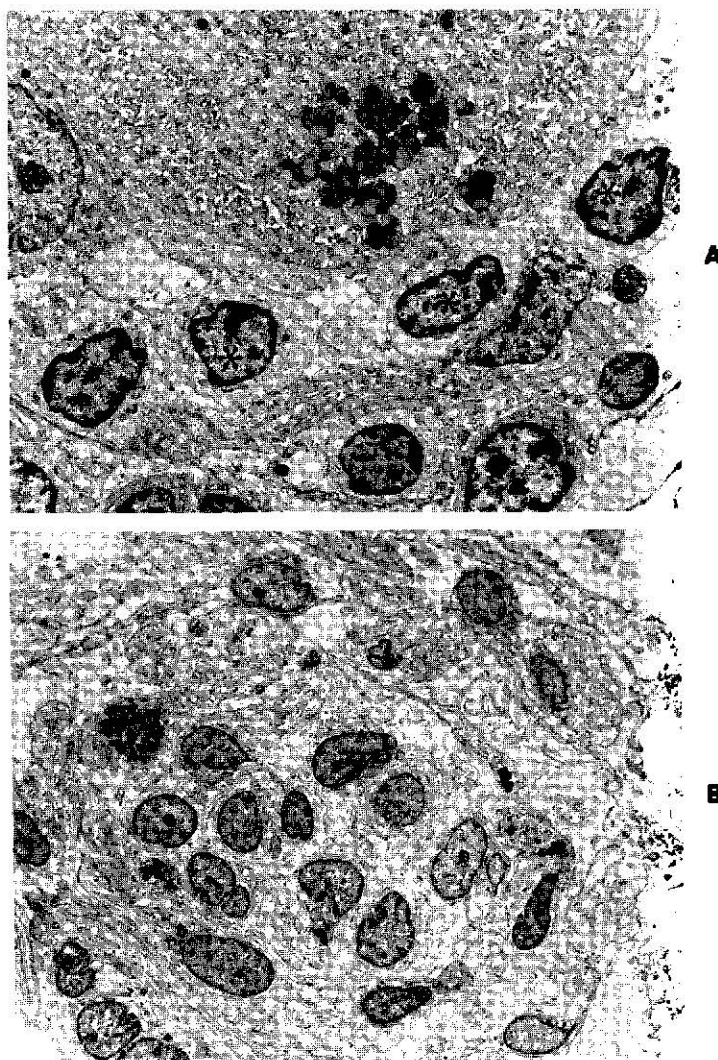


Fig. 7-16. Canine ganglionic radiculitis. **A**, Lymphocytes (asterisks) displace satellite cells and abut ganglion cell, which contains lipofuscin granules. ($\times 3900$.) **B**, Nageotte nodule—proliferated satellite cells—and a few macrophages with granular debris. ($\times 1300$.)

especially of the lung.⁶⁻⁹ In ganglioneuritis associated with carcinoma or sensory neuropathy preceded by antibiotic therapy¹⁰ or in other idiopathic forms of human sensory neuropathy,^{11,12} the usual etiological speculations include viral and immune mechanisms. Sensory ganglionitis and neuron degeneration also occur in humans in association with Sj gren's syndrome, a disorder characterized by keratoconjunctivitis sicca, dry mouth, and evidence of connective tissue disease.¹³ Ganglion biopsy studies reveal that lymphocytes and macrophages infiltrate around individual sensory neurons. These images of T-cell inflammation suggest that the spinal ganglia are extraglandular sites for autoimmune attack. Similar images of lymphocytes and macrophages displacing satellite cells and encroaching upon

ganglionic cell bodies in affected dogs indicate that these neurons also are the prime targets of the pathological process. What incites this process remains to be defined, although T cell-mediated neuronal damage seems as plausible in these dogs as in human patients.¹⁴

References are on page 489.

ENTERIC GANGLIONITIS

Inflammation of the enteric nervous system occurring independent of CNS and PNS involvement has been reported only rarely in domestic species. Idiopathic **myenteric ganglionitis** was described in a 2-year-old female Border Terrier with atropine-insensitive bradycardia, dysphagia, esophageal weakness, and extremely fast small intestinal transit time.¹ Megaesophagus was confirmed at necropsy. Microscopic examination revealed nonsuppurative leukocytic infiltration of the myenteric plexus of the esophagus, stomach, small intestine, and, to a lesser extent, the colon. Lymphocytes predominated in these infiltrates, which varied in severity, but were associated with enteric neuronal degeneration. The cause of this enteric ganglionitis remained unknown.

Köhler and Hein,² in a postmortem study of seven horses with colic and eight healthy animals, observed leukocytic infiltrates in the colonic myenteric ganglia of only the affected animals. The neutrophils in these infiltrates were regarded as evidence of inflammation; the lymphocytes around ganglia, however, were perceived as possibly not being abnormal. More recently, in a 4-year-old Standardbred mare, small colon impaction recurred as a manifestation of pseudo-obstruction.³ Pseudo-obstruction has been characterized by symptoms and signs of intestinal obstruction in the absence of mechanical blockage.⁴ Chronic pseudo-obstruction has resulted from disorders of intestinal smooth muscle or the enteric nervous system. In this horse a biopsy sample of the small colon taken during surgical relief of the impaction revealed myenteric ganglionitis. Mononuclear leukocyte infiltration and neuronal degeneration and loss occurred in both the myenteric and submucosal plexuses. In samples of small colon taken 2 weeks later at necropsy, the leukocytic infiltration was less striking. There was, however, developing fibrosis in the region of the myenteric ganglia. Leukocytic infiltrates were also observed in the cranial mesenteric ganglion.

In a 4-year-old postpartum cow, colonic and cecal distension and intestinal atony were associated with an idiopathic submucosal and myenteric ganglionitis.⁵ In this bovine case of chronic pseudo-obstruction, leukocytic infiltrates and neuronal degeneration occurred in the cranial mesenteric ganglion as well as in enteric ganglia.

It is strongly suspected that the prevalence of intestinal pseudo-obstruction in domestic animals due to degeneration or inflammation of enteric neurons is much greater than the few reports in the literature suggest. A higher incidence and wider array of myenteric neurological disorders are also

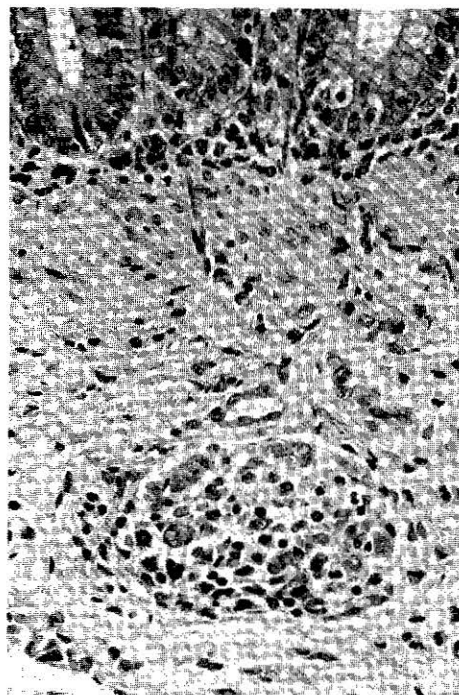


Fig. 7-17. Ganglionitis of submucosal plexus in colon, dog. *Trypanosoma cruzi* infection. (H&E, $\times 350$.)

thought to go undetected in human beings.⁴ The preceding bovine and equine cases of pseudo-obstruction may have counterparts in the idiopathic cases of chronic myenteric plexitis identified in humans.

Although the preceding disorders were in domestic species and occurred exclusive of CNS involvement, inflammation and degeneration of the intestinal myenteric plexus occurred in two giraffes with listeriosis and multifocal suppurative leukoencephalitis and myelitis.⁶ The chronic wasting syndrome caused by this myenteric ganglioneuritis affected additional giraffes from which *Listeria monocytogenes* could not be isolated. It was suspected that listeriosis was coincidental with idiopathic enteric ganglionitis.⁷ We have observed enteric ganglionitis in a case of canine trypanosomiasis (Fig. 7-17).

Myenteric ganglionitis and encephalomyelitis have been associated with anorexia, weight loss, depression, changes in fecal consistency, proventricular dilation, regurgitation, and death in **psittacine birds**.^{8,9} Nonsuppurative infiltrates with lymphocytes, plasma cells, and macrophages have been found in the myenteric plexus in the proventriculus, ventriculus, and descending duodenum of affected macaws. The etiology is unknown. The presence of eosinophilic inclusion bodies in the nuclei and cytoplasm of neurons has suggested a viral cause. Despite ultrastructural demonstrations of paramyxoviral-like particles,⁸ no virus has been isolated to date.

References are on page 489.

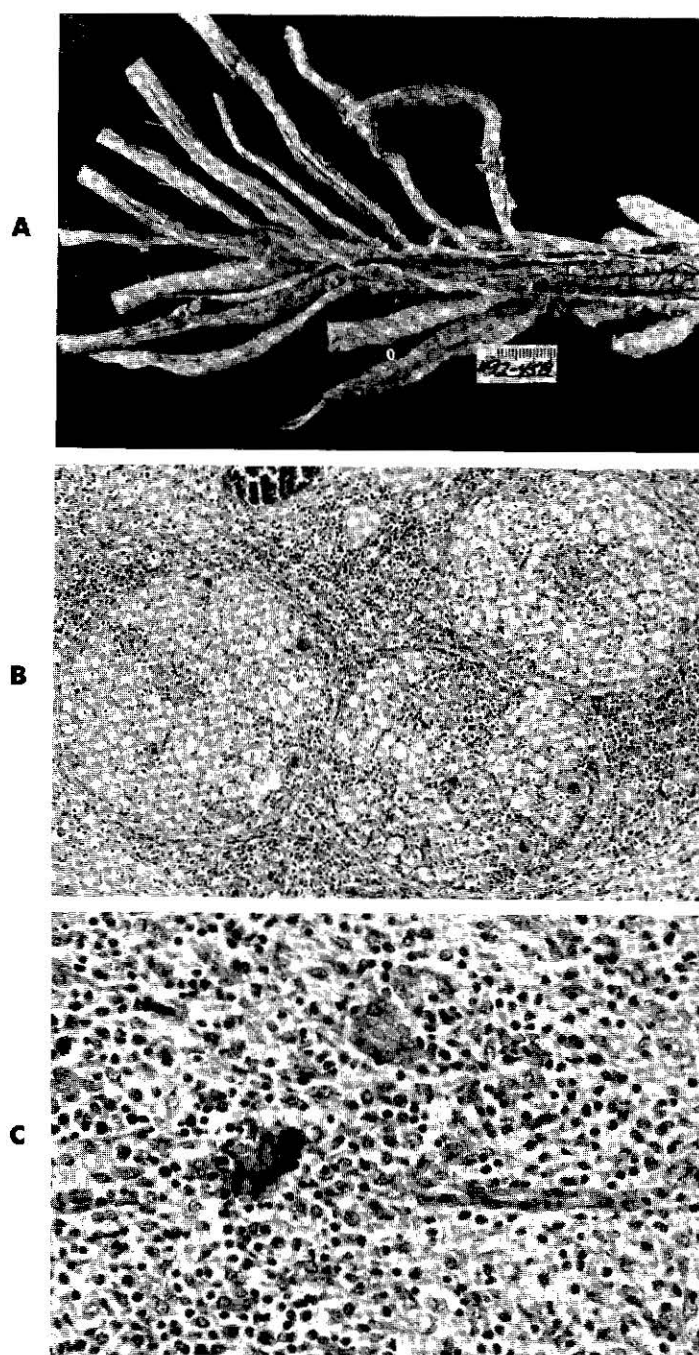


Fig. 7-18. Neuritis of the cauda equina, horse. **A**, Massively thickened extradural spinal roots and nerves of the cauda equina. **B**, Three nerve fascicles in the cauda equina are obscured by inflammation within and between fascicles. (H&E, $\times 140$.) **C**, Giant cells, lymphocytes, plasma cells and macrophages within a nerve fascicle. (H&E, $\times 350$.)

NEURITIS OF THE CAUDA EQUINA

In 1897, Dexler described a rare combination of tail and sphincter paralysis in the horse that resulted from chronic inflammation of the extradural portions of the nerve roots of the cauda equina.¹ Since Dexler's study, many similarly affected horses and ponies have been studied in Europe and more recently in North America. Adult horses of all breeds are affected; the youngest recorded case occurred in a 17-month-old Saddlebred filly.² Many of the clinical findings, which include perineal paresthesia with rubbing and hair loss followed by perineal anesthesia, urinary incontinence, fecal retention, tail paralysis, croup muscle atrophy, and hind limb ataxia and weakness, are referable to the sacrocaudal spinal segments. Lumbar and other root levels may also be affected, and signs of cranial nerve involvement (e.g., facial paralysis, head tilt, and wasting of the masticatory muscles) are not uncommon.³⁻¹¹ The more widespread involvement of spinal roots and cranial nerves has suggested the alternate name **polyneuritis equi**.¹² Complete blood counts often reveal a neutrophilic leukocytosis, and CSF samples may be expected to contain elevated protein levels and increased white blood cells.¹³ Treatment with antibiotics and/or corticosteroids has proved futile, and owners generally request that the animal be destroyed as the neurological deficits persist unabated.

Gross necropsy findings include striking thickening, hemorrhagic discoloration, and fibrosis of the extradural portions of the nerve roots emanating from the last lumbar, sacral, and caudal segments of the spinal cord (Fig. 7-18, A). The thickening is prolonged through the spinal nerves and often along the initial course of the peripheral nerves. Regional macroscopic swelling may be detected in various

peripheral and cranial nerves.¹⁴ More proximally, the intradural roots of the sacrocaudal segments are usually discolored, but only exceptionally have they been as notably thickened as the extradural portions.

The changes in the extradural roots and spinal ganglia include marked granulomatous inflammation and proliferation of the epineurial and perineurial nerve sheaths. Granulomatous changes may even be encountered in autonomic ganglia.¹⁵ Nerve fascicles are variously affected at the extradural root level and beyond. Some remain intact, and others have dense infiltrates of lymphocytes, plasma cells, and macrophages in the perineurium that extend in moderate numbers into the fascicle interior. Some nerve fascicles may contain microabscesses. Other fascicles are infiltrated very extensively by lymphocytes, macrophages, and plasmacytes and sustain great loss of nerve fibers (Fig. 7-18, B and C). In these nerve bundles, centrally located giant cells and epithelioid cells may also be part of the prominent granulomatous lesions. Within some fascicular outlines, axons and associated Schwann cells appear to have been replaced by organized granulation tissue.

Although they are usually less severely affected, the intradural roots and their sheaths also contain mononuclear cell infiltrates (Fig. 7-19). Axon damage is decidedly less prevalent at this proximal level, but segmental myelin loss is encountered in the infiltrated areas. Often demyelination is associated with invading macrophages, which appear to strip the myelin lamellae. On rare occasions, macrophages also appear between a swollen loosened myelin sheath and a condensed axon. Some myelin sheaths seem to undergo swelling, splitting, and vesicular degeneration in the absence of invading leukocytes. Degrading axons are encountered, but more commonly sites of earlier axon loss are marked by Büngner's bands. These proliferated Schwann cell cords, however, are much more abundant in the extradural roots. Some evidence of regeneration may be encountered in the roots in the form of axon sprouts or in the more advanced form of clusters of regenerating axons.

As a consequence of axon interruption in the roots, retrograde chromatolysis develops in the somatic motor neurons of the affected spinal segments. Destruction of primary sensory neurons in the dorsal roots and ganglia leads to orthograde fiber degeneration in the spinal dorsal funiculus.

In several studies, neuritis of the cauda equina (NCE) has been compared to the Guillain-Barré syndrome (GBS) in humans and to experimental allergic neuritis (EAN) in laboratory animals.^{9,16,17} These comparisons are justified by certain findings. As described in GBS and EAN, the demyelinating changes in the proximal roots in NCE are often associated with invading mononuclear cells and macrophages that strip away segments of the myelin sheath.¹⁰ Cellular stripping, however, is a non-specific form of demyelination¹⁸ and is not pathognomonic of a cell-mediated, immune response directed against myelin antigen.¹⁹ Nevertheless, comparison with EAN is made more com-

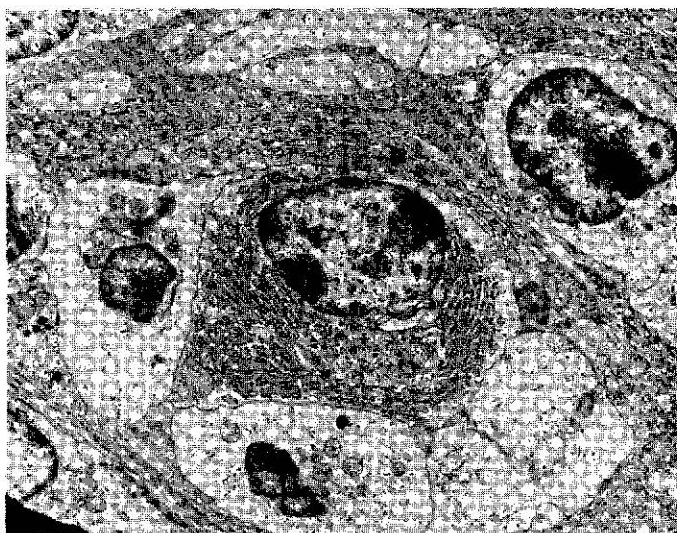


Fig. 7-19. Neuritis of the cauda equina, horse. Cluster of lymphocytes and a plasma cell. ($\times 5850$.)

elling by the demonstration in NCE of circulating antibodies against P₂ myelin protein, a neuritogenic myelin antigen that on injection produces EAN.^{14,20,21} It remains to be determined whether these circulating antibodies play a primary role in demyelination or represent a consequence of antigen released in the course of myelin destruction. Comparisons with the GBS and EAN are made tenuous by some contrasting clinicopathological features of NCE, which include its chronic unremitting course, the intense granulomatous inflammation of the extradural roots, and the prevalence of axon degeneration. Although NCE has been viewed as a post-infectious allergic neuritis, attempts to identify a specific agent had failed until 1984, when equine adenovirus I was isolated from two of three cases of NCE.²² This isolation suggests that NCE may be an autoimmune radiculoneuritis initiated by a viral infection.

References are on page 489.

PROTOZOAN POLYRADICULONEURITIS

Three different clinical forms of toxoplasmosis have been identified in young dogs.¹ These include generalized, central nervous, and radiculoneuritic forms. The last form has occurred in pups under 3 months of age and is thought to be a congenital infection. *Toxoplasma* radiculitis in pups has presented with a fairly characteristic group of clinical findings.¹⁻⁶ Typically, affected pups become acutely paraparetic with the limbs fixed in rigid extension. Hindlimb muscles are firm on palpation. Patellar and withdrawal reflexes are

lost. These clinical findings have led to a description of the paresis as partially spastic and partially flaccid.¹ Pain sensation persists. Pups experience pain over the back and hindlimbs on movement, and palpation of the hyperextended stifles may evince signs of discomfort. Electrodiagnostic studies reveal spontaneous denervation potentials, and delayed motor nerve conduction velocities may or may not be recorded.^{5,6} After the acute, progressive stage, signs stabilize. There is no improvement, and wasting in the hindlimbs becomes more obvious. Although the radicular form of toxoplasmosis is extremely incapacitating, it usually is not fatal.

Diagnostic confirmation of *T. gondii* infection may be provided by various serological procedures including complement fixation, indirect hemagglutination, indirect fluorescent antibody, and the Sabin-Feldman dye tests.⁷ Tissue techniques include organism isolation, brain tissue injection in laboratory or other species, and various immunocytochemical procedures.⁷⁻⁹

At necropsy, there is distinct atrophy and discoloration in the hindlimb musculature. Although organisms, inflammatory changes, and necrosis are demonstrable microscopically in brain, spinal cord, and skeletal muscles, the most intense lesions occur in the roots of the lumbosacral spinal cord. The roots contain prominent perivascular and interstitial infiltrates composed of lymphocytes, plasma cells, and macrophages (Fig. 7-20). Ventral roots may be more severely involved. Protozoan organisms appear in parasitophorous vacuoles or pseudocysts, which may not be in

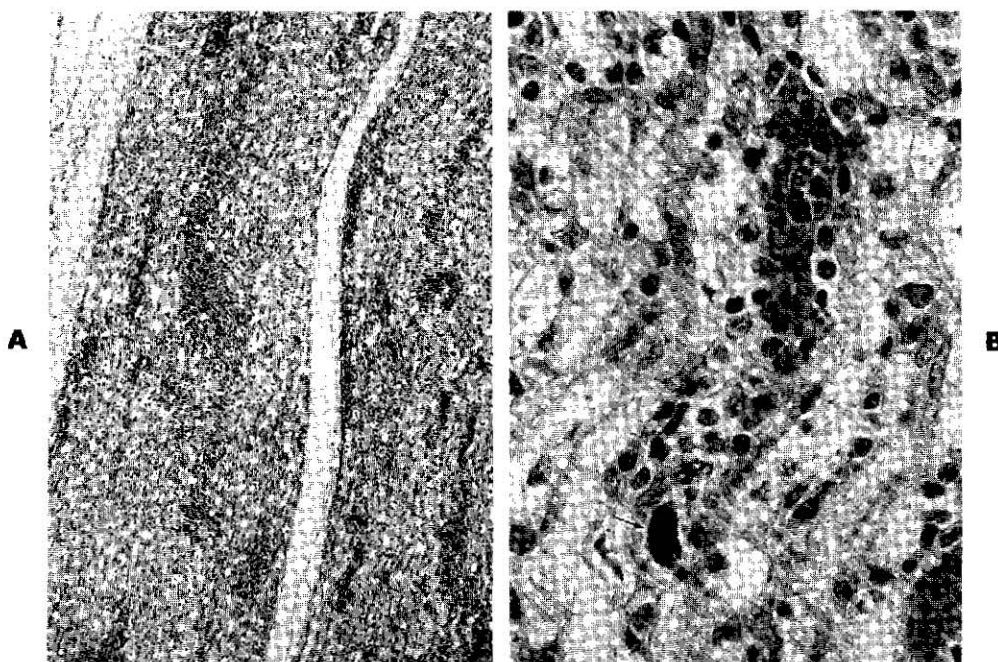


Fig. 7-20. Protozoan radiculoneuritis, dog. **A**, Lumbar spinal roots: nonsuppurative inflammation and degeneration of the nerve. (H&E, $\times 140$.) **B**, Small perivascular cuff and cluster of protozoal organisms (arrow). (H&E, $\times 715$.)

the areas of intense inflammation.⁶ Radicular axons are affected variously; they may appear interrupted, swollen, or demyelinated.^{1,4,6} Although the radicular changes are considered chiefly responsible for the clinical deficits, these effects are compounded by the accompanying encephalomyelitis and myositis.

Studies in dogs in Europe had indicated that there was another cyst-forming sporozoan parasite that simulated *T. gondii* in producing encephalomyelitis, meningomyelitis with radiculitis, and myositis in dogs.⁹⁻¹¹ In the United States, a similar *Toxoplasma*-like organism had been associated with a fulminating polyradiculoneuritis in four of a litter of eight unweaned Labrador Retriever pups.¹² The clinical picture differed from the radiculoneuritis typically reported in pups with *T. gondii*.¹³ These pups suddenly developed asymmetric paraparesis, which quickly became symmetric, and in 3 days progressed to flaccid tetraplegia with cervical paralysis, inability to prehend food, and dysphagia. Death ensued rapidly, presumably because of respiratory failure.

As in toxoplasmosis, microscopic study of the brain and spinal cord revealed a multifocal, nonsuppurative meningoencephalomyelitis. Small microglial nodules marked focal areas of necrosis, and pseudocysts contained large numbers of fusiform or crescentic organisms. These diffuse CNS changes were overshadowed, however, by an intense polyradiculoneuritis that affected the spinal roots and nerves at virtually all segmental levels, as well as many of the cranial nerves. Extensive infiltrates consisted of lymphocytes, macrophages, and plasma cells. Neutrophilic and eosinophilic foci also occurred. The spinal ganglia contained fewer infiltrates than the dorsal roots, which were often less severely affected than the ventral roots. Elongate pseudocysts with many organisms paralleled the axons in the spinal roots and nerves. Many myelinated axons were degenerated. Axon fragments and myelin ovoids formed linear series of digestion chambers. On transverse sections of the roots, many swollen axons were encountered, and most of these had lost their myelin sheaths. Among the surviving myelinated axons, there were some in which the associated Schwann cells had undergone a remarkable vacuolar destruction. The microscopic appearance of the lesions and organisms suggested an overwhelming form of toxoplasmosis. This diagnosis, however, could not be confirmed by serological, immunocytochemical, or ultrastructural diagnostic procedures.¹² Similar negative diagnostic findings for *T. gondii* had occurred with a *Toxoplasma*-like organism that had been discovered previously in dogs in Scandinavia.^{9-11,14,15} In subsequent investigations on a second litter of neonatally infected Labrador pups from the same bitch, the offending protozoan organism was identified as *Neospora caninum*.¹⁶ Retrospective immunocytochemical studies on tissues of many dogs that had had postmortem diagnoses of toxoplasmosis indicated that this newly recog-

nized parasite, *N. caninum*, commonly had been confused with *T. gondii*.^{17,18} *Neospora* organisms, recovered from affected pups and isolated in cell cultures, produced widespread disease when inoculated in a control dog. Transplacental *N. caninum* infection also has been induced experimentally in dogs.¹⁹

Electron-microscopic studies of the tachyzoites of this newly identified organism (references 9, 10, 12, 14, 15, 17, 20) have demonstrated ultrastructural features that differ slightly from those typically ascribed to *Toxoplasma*.^{21,22} In our experience, the greater numbers of both rhoptries and micronemes in this organism constitute the most easily perceived basis for making a ultrastructural distinction from *T. gondii*. Electron microscopic study also revealed that the invading and proliferating tachyzoites of *N. caninum* can play a direct role in the induction of peripheral nerve lesions.¹² Tachyzoites invaded both Schwann cells and axons. In contrast to some ultrastructural descriptions of *Neospora*,^{17,23} we have not seen intracellular tachyzoites free in the cytoplasm; rather, they have appeared within distinct parasitophorous vacuoles.¹² Proliferation of the tachyzoites, through the process of endodyogeny, expanded the individual Schwann cells greatly (Fig. 7-21) and ultimately caused their death through vacuolar disruption. In the wake of this disruption, only the encircling basal lamina persisted and retained necrotic Schwann cell fragments and degenerated organisms. This vacuolar form of Schwann cell destruction would eventuate in segmental myelin loss, but through a constrictive effect might also lead to axon atrophy or degeneration. In this regard, there were Schwann cells that were greatly distended by parasitophorous vacuoles, and no trace of axon or myelin remained. More widespread evidence of axon degeneration appeared in the form of B  nner's bands. These were abundant, and the lack of axon sprouts within them indicated that there was little regeneration in the early stages of this radiculitis.

The tachyzoites of the organism also invaded axons. Invaded axons were swollen by masses of misdirected neurofilaments. These greatly enlarged axons closely resemble those induced by toxic impairment of slow axonal transport.²⁴ This resemblance suggested that intraneuronal organisms may physically or otherwise interfere with axon transport and thus establish conditions that lead to axon swelling and degeneration.

Although *N. caninum* appeared to differ from *T. gondii* in producing a more fulminating polyradiculoneuritis and in its serological, immunocytochemical, and EM characteristics, the histological appearance of the lesions was remarkably similar to that of toxoplasmosis. This lesion similarity suggests that *Neospora*, with its unknown host range and life cycle, may continue to be confused with *Toxoplasma*. In this regard, it should be noted that in one recent case with signs typical of radiculoneuritic toxoplasmosis—a pup with paraplegia in rigid extension—serological and

immunocytochemical procedures were negative for *T. gondii* but positive for *N. caninum*.²⁵ Dubey and co-workers²⁶ believe that most reported cases of ascending paralysis in dogs that had been diagnosed as toxoplasmosis were actually caused by *N. caninum*. Much remains to be learned about this *Toxoplasma*-like organism that has been found in spontaneous cases of fatal myelitis in newborn calves.²⁷

References are on page 490.

GRANULOMATOUS RADICULITIS OF THE SEVENTH AND EIGHTH CRANIAL NERVES IN CALVES

Outbreaks of persistent, unilateral, facial paralysis have been described in 2- to 6-month-old calves in France,¹ Belgium,^{2,3} and South Africa.⁴ These animals developed a drooping ear and lower lip and were unable to close their eyelids on the affected side. The latter deficit led to the development of purulent keratoconjunctivitis in some animals.² In one outbreak involving 16 calves, head tilt on the side of the facial hemiplegia indicated concurrent involvement of the vestibulocochlear nerve.³

At necropsy, space-occupying, nodular granulomas com-

monly were associated with the intracranial roots of the facial and vestibulocochlear nerves. These masses were said to vary from the size of a pea to that of a walnut. Occasionally, cranial nerve roots other than the facial and vestibulocochlear nerves were also affected. Microscopic examination of the space-occupying lesions revealed mainly histiocyte cells, some plasma cells, and multinucleated giant cells. Degenerating myelinated and unmyelinated fibers were seen within the nodular masses. The etiology of these reported outbreaks was not determined, although an association with otitis media was suggested.⁴

Thus far, attempts to isolate an infectious agent have been unrewarding. Whereas the granulomatous lesions have been compared to those encountered in neuritis of the cauda equina in horses, similarities have also been noted to histiocytic tumors.

References are on page 490.

CRANIAL NEURITIS WITH GUTTURAL POUCH MYCOSIS AND EMPYEMA IN THE HORSE

The guttural pouch is an extensive, thin-walled, ventral diverticulum of the equine auditory tube that is situated

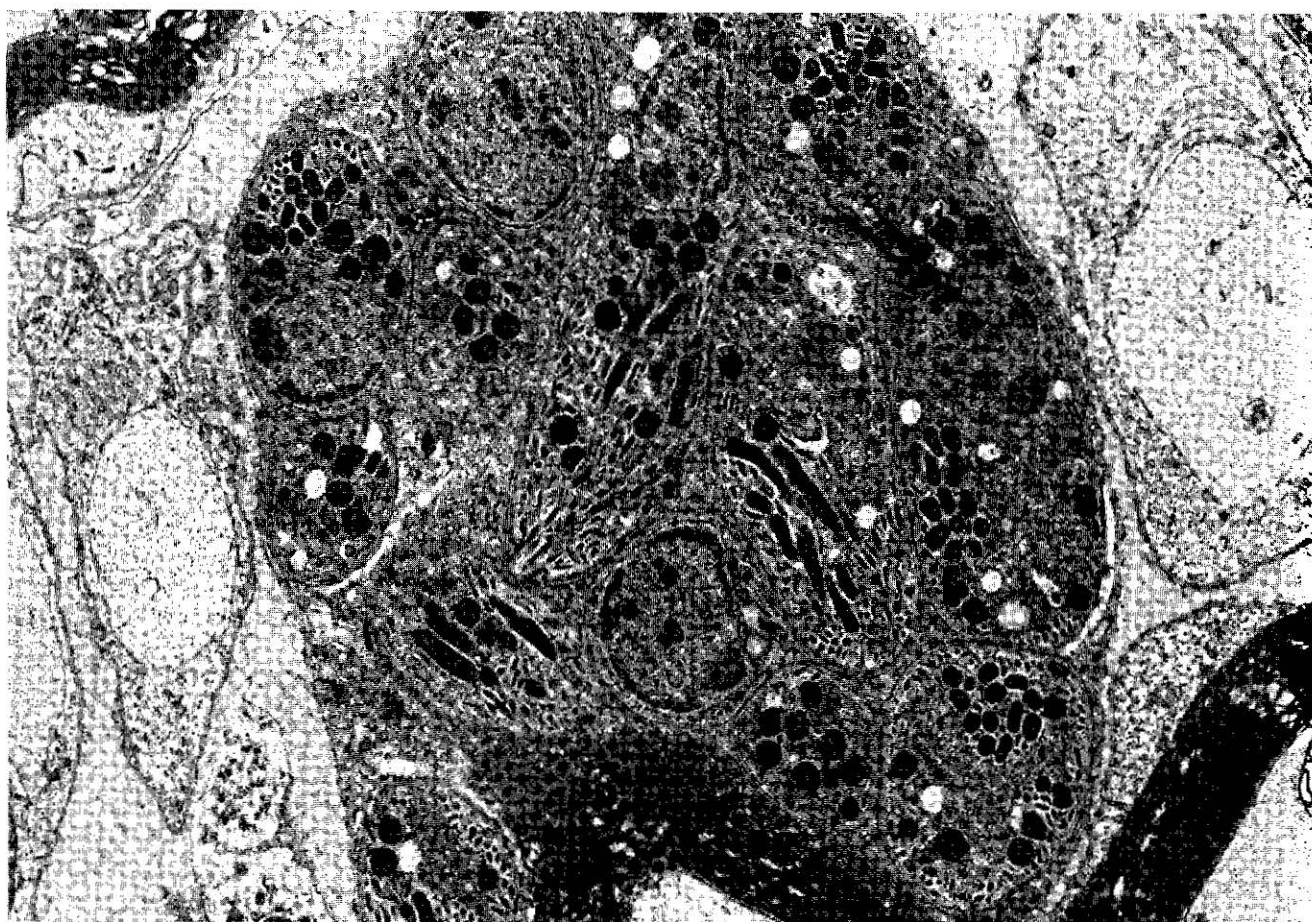


Fig. 7-21. Protozoan radiculoneuritis, dog, *Neospora caninum* tachyzoites within the cytoplasm of a Schwann cell. ($\times 18,460$.)

between the base of the skull dorsally and the pharynx ventrally. Mycotic, diphtheritic inflammation of the dorsal wall of the medial compartment of the guttural pouch frequently results in mucopurulent nasal discharge, epistaxis, and dysphagia.^{1,2} The glossopharyngeal nerve and pharyngeal branch of the vagus are closely associated with the caudodorsal and lateral walls of the medial compartment of the guttural pouch.³ Involvement of the pharyngeal branches of the glossopharyngeal and vagus nerves by mycotic inflammation at this level leads to ipsilateral hypesthesia of the pharyngeal mucosa and pharyngeal paresis with regurgitation.⁴ Laryngeal hemiplegia occurs on the left and results from involvement of the fibers that will form the recurrent laryngeal nerve while they are still within the parent vagal nerve.⁵ When the internal carotid nerve, which contains postganglionic sympathetic axons to the head, is also affected, Horner's syndrome results. With extensive inflammation, the adjacent facial nerve may be affected also. Vestibular nerve involvement has occurred only rarely.³ Blindness, which has been observed sometimes, is thought to reflect involvement of the carotid artery.² Associated with the inflammation, hyperplastic changes and exostoses develop on adjoining bony structures, for example, the tympanic bulla, external auditory meatus, the muscular process of the petrous temporal bone, and the proximal end of the great cornu of the hyoid bone.

Microscopic study of affected nerves has revealed active

neuritis. The involvement has varied from slight swelling of myelin sheaths and Schwann cells with dilation of intraneural capillaries to heavy leukocytic infiltration of the nerves and outright necrosis with fungal penetration. Chromatolysis and degenerative swelling and vacuolation of neurons have been found within the cranial cervical ganglia in some animals.⁵

Initially, it was suspected that fungus, an *Aspergillus* species, reached the pouch via the pharyngeal orifice of the auditory tube and, alone or together with bacteria, provoked an inflammation that commonly lead to erosion of the internal carotid artery and epistaxis.⁵ More recent work, however, suggests that hemorrhage results from aneurysms that develop along aberrantly bifurcated internal carotid arteries.⁶ This primary arterial disease may predispose to secondary infection by fungus or bacteria. Ligation of the internal carotid artery on the cardiac side of the vascular lesion has provided effective treatment. In one study,⁷ 23 of 30 affected horses recovered completely after ligation. Total recovery from pharyngeal paralysis in a high percentage of horses suggested that this deficit in many cases stems largely from neuropraxia, rather than necrotizing inflammation of nerve fascicles.⁷

Suppurative inflammation of the pouch that progresses to empyema and produces dysphagia usually occurs after respiratory infection with *Streptococcus equi*.²

References are on page 490.

Degenerative diseases of the peripheral nervous system

CANINE INHERITED HYPERTROPHIC NEUROPATHY

This demyelinating neuropathy, which produces primitive onion bulb configurations, is a recessively inherited defect in **Tibetan Mastiffs**.^{1,2} Although this defect seemed to represent a problem in American-bred dogs, affected pups have been identified in Switzerland and, more recently, in Australia.^{3,4} Typically, the onset of signs occurs at 7 to 10 weeks of age and is marked by hindlimb gait abnormalities and weakness that progress quickly to involve the forelimbs. Severely affected pups become tetraparetic within 3 weeks and are unable to rise from sternal recumbency. Patellar reflexes are usually lost, and pedal reflexes are depressed. Clinical evidence of cranial nerve impairment has been limited to dysphonia. Recumbent pups may develop sternal compression and limb contractures in addition to some reduction in muscle mass. Some pups after 6 to 7 weeks regain the ability to rise, but they and other affected pups that

remained ambulatory are plantigrade and have a slow, shuffling gait. Affected pups raised to adulthood show little or no improvement. Electrodiagnostic studies have revealed transient denervation potentials in most affected pups.⁵ Motor and sensory nerve conduction velocities are slowed as the disease progresses, and the amplitude of the evoked muscle responses is reduced.

In accordance with the clinical findings, pathological changes occur most abundantly in the spinal roots and peripheral nerves and reflect an inability of the Schwann cells to form and maintain a stable myelin sheath. That the defect resides in the Schwann cell and not in the axon has been demonstrated in the nerve transplant studies of Cooper and colleagues.⁶ Ultrastructurally, the degeneration is characterized by changes that usually appear in the cytoplasmic regions of the myelin sheath. These include separations at the major dense lines, anomalous incisure patterns, and filamentous accumulations in the inner sheath spirals and

adaxonal cytoplasm (Fig. 7-22). Incisure or cleft-like, uncompacted regions of the myelin are often asymmetrically developed and abnormally oriented. These incisures abnormalities occur in sheaths undergoing initial degeneration as well as those that have been restored through remyelination. Many myelin sheaths are marked internally by accumulations of 6- to 7-nm cytoplasmic filaments. These filaments contain actin⁷ and frequently are massed to the point where they distend the inner myelin lamellae and the adaxonal Schwann cell cytoplasm. In some accumulations, the filaments are mixed with a dense, finely granular material. Some ultrastructural images strongly suggest that inward expansions or incursions of these filamentous regions may

constrict or subdivide the axon. The filament masses, through compression and distortion, may interfere with axon transport, and the incursions may serve as partitions that create blind recesses along the axon. These recesses appear identical to the axonal outpocketings described in equine recurrent laryngeal nerves.⁸ The outpocketings in the equine nerve, however, result not from incursions of the myelin sheath, but from protrusions of the paranodal axon that accumulate organelles to the point where they cause splits in the myelin sheath.

Degenerating myelin sheaths in the Tibetan Mastiff pups are commonly invaded by macrophages. Naked axons are encompassed often by two Schwann cells as a result of the

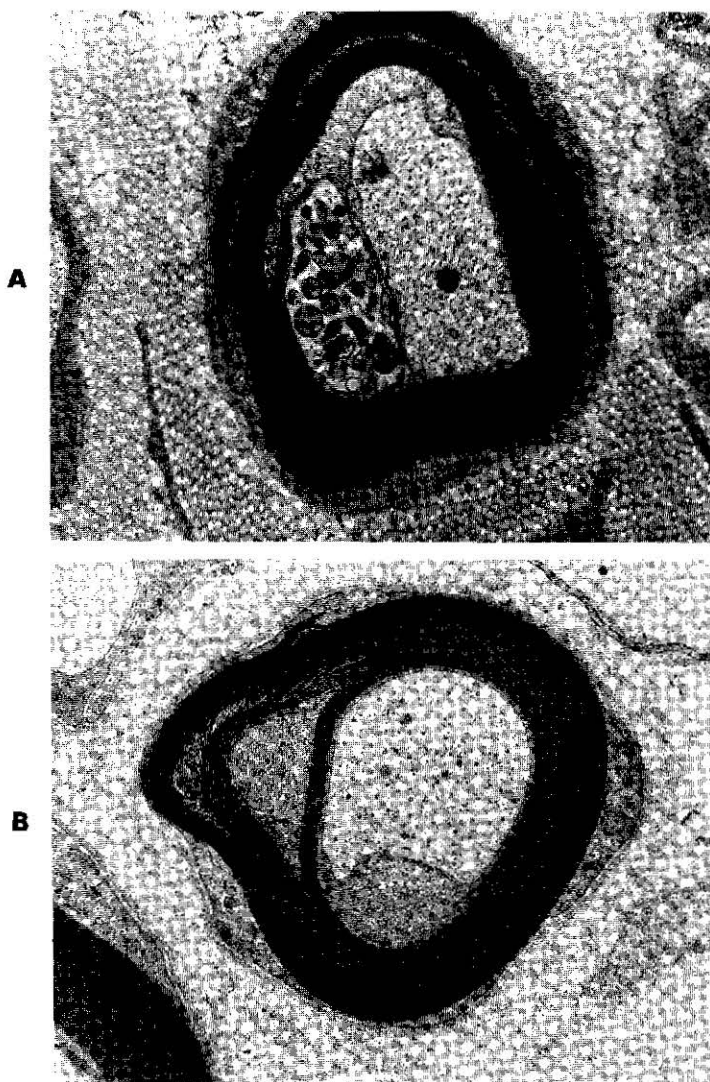


Fig. 7-22. Canine inherited hypertrophic neuropathy. **A,** The Schmidt-Lantermann incisure is abnormal in its disposition. The axon has been partitioned by an incursion of Schwann cell cytoplasm. The smaller axon profile contains mitochondria and lysosomal dense bodies. ($\times 18,750$.) **B,** Inner loop and incisured accumulation of filaments distort transected axon profile. ($\times 26,000$.)

proliferation of these cells that occurs in the wake of demyelination. Further evidence of Schwann cell proliferation may be found in large numbers of primitive onion bulbs wherein a central axon, often with a thin myelin sheath, is surrounded by satellite Schwann cell processes (Fig. 7-23). Although some of these processes may be lateral projections of the central remyelinating cell, others clearly belong to redundant, peripheral Schwann cells.

Although the primary defect in these dogs resides in the Schwann cell, there is clinical, electrical, and morphological evidence of axon degeneration. In pups, only occasional examples of atrophic axons and Büngner's bands are found, although peripheral nerve biopsies from affected adults reveal greater loss of large myelinated axons and notable endoneurial fibrosis. To what extent the axon damage is inflicted by swellings or incursions from abnormal sheaths is a matter for additional study. In this regard, it is interesting to note that in the trembler mouse, a similar but dominant dysmyelinating mutant, the defect is associated with altered slow axonal transport of neurofilaments and slower axon regeneration.⁹ Moreover, by grafting heterologous trembler nerve segments into control sciatic nerves, the abnormal Schwann cells were shown to locally modify axon caliber, neurofilament organization, and slow axonal transport.¹⁰ Mutations of the gene for the newly defined myelin protein, peripheral myelin protein 22 (PMP 22), have been implicated in the pathogenesis of the trembler neuropathy and the human hypertrophic neuropathy of Charcot-Marie-Tooth.¹¹ Clearly, PMP 22 is a logical focus for future investigations of this canine hypertrophic neuropathy.

References are on page 490.

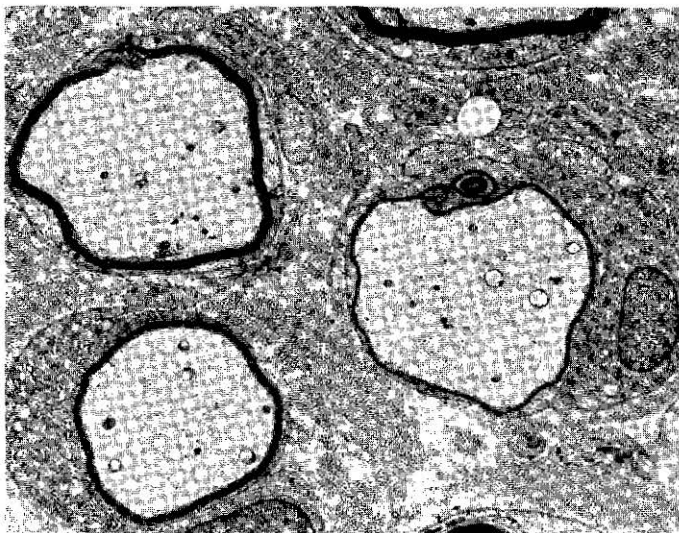


Fig. 7-23. Canine inherited hypertrophic neuropathy. Thinly myelinated axons within primitive onion bulbs. ($\times 5850$.)

HYPERTROPHIC POLYNEUROPATHY IN THE CAT

Hypertrophic polyneuropathy has also been encountered in cats. Dahme, Kraft, and Scabell¹ reported a progressive neurological disorder marked by tremors in two unrelated, non-purebred cats. At 1 year of age, signs, in addition to intention tremor, included unsteady gait, uncontrolled urination and defecation, low-grade sensory abnormalities, reduced tendon reflexes, and deficient or uncertain postural reactions. The authors recorded depressed leukocyte and platelet counts and elevated blood glucose levels in one cat. A CSF sample yielded a positive Pándy reaction.

At necropsy, the only grossly discernible change occurred in the peripheral projections of the cerebrospinal and autonomic nervous systems. All of the roots of the cerebrospinal nerves, both motor and sensory, had a glassy gray appearance and were thickened 3 to 5 times normal diameter. The nerve enlargement persisted distally and could be traced into the finest terminal branches. In the swollen nerves, there were gelatinous, mucoid masses in a subperineurial position. This gelatinous material was lacking in the enlarged autonomic nerves (e.g., the sympathetic trunk), which had an unusually firm consistency.

Microscopically, there were major changes in the myelin sheaths and perineurium. The myelin sheaths were greatly reduced in the cranial and peripheral nerves and roots; the axons appeared undamaged at the light microscopic level. With the regression of the myelin sheaths, there was proportional development of onion bulb configurations. These consisted of concentric arrays of Schwann cells around an axial axon. These onion bulbs were separated by densely arranged endoneurial collagen. The central axons appeared reduced in diameter and contained densely arranged neurofilaments. Few or no changes were detected in the Schwann cells of unmyelinated autonomic axons, although preganglionic fibers had undergone onion bulb transformations. In the larger peripheral nerves, accumulations of mucoid material were prominent between the inner cell layers of the perineurium and between the perineurium and the nerve fibers. This material had an amorphous or finely granular ultrastructural appearance.

On the basis of purely morphological criteria, this feline hypertrophic neuropathy appeared comparable to hereditary motor and sensory neuropathy, type I, in humans.² The underlying pathogenetic mechanism in these two unrelated cats with hypertrophic neuropathy is unknown. The likelihood of an inherited defect seemed diminished because the affected cats were neither related nor members of a recognized breed. Acquired causes, for example, infectious and toxic, could not be eliminated from consideration.

At Cornell, a single case of feline hypertrophic neuropathy has been observed. As in the two cases recorded by Dahme and co-workers,¹ this castrated male domestic cat was presented at the clinic at 1 year of age with generalized tremors that grew worse with activity. The signs were noted

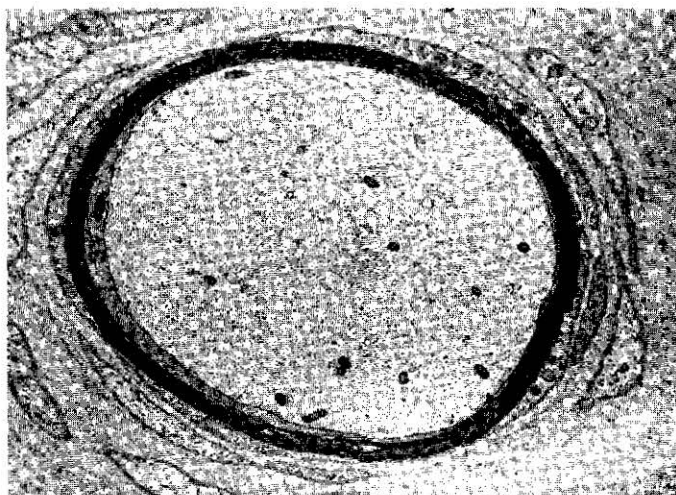


Fig. 7-24. Hypertrophic neuropathy, cat. Onion bulb. ($\times 9100$.)

first at 7 months. When the cat walked, the hind limbs were widely abducted, and there was marked tarsal flexion so that the animal's gait, in essence, was plantigrade. Occasionally, the cat knuckled on the hind paws and the hind limbs would slide out from under him. The forelimb gait was spastic and hypermetric. Pain perception was blunted over the paws, face, and in the nasal vestibule. On re-examination 3 months later, the cat was even more ataxic; generalized tremors persisted and were clearly intensified by exercise. The animal's strength was good. The only observed muscle atrophy was mild and confined to the muscles of mastication.

At necropsy, the most notable changes occurred in the cranial and peripheral nerves and the spinal cord. In the cranial and peripheral nerves and roots, virtually all of the larger axons appeared thinly myelinated or demyelinated and were incorporated in small onion bulb configurations (Fig. 7-24). At the ultrastructural level, many of the thinly myelinated sheaths appeared to be loosely arranged and degenerating on their inner or axonal aspect. The adaxonal Schwann cytoplasm and the inner lamellae often contained accumulations of fine filaments. These cytoplasmic filaments resembled those that accumulate in the inherited hypertrophic neuropathy of Tibetan Mastiffs.³ As in the latter neuropathy, there were also accumulations of a dense granular material that accompanied the filamentous aggregates and perhaps were derived from them. The buildup of the filamentous and granular material in the inner cytoplasmic region of the myelin sheath often was so extensive that it distorted the axon. Sometimes the axons were abutted and possibly compressed by macrophages that were intercalated between axolemma and the remaining myelin lamellae. Despite the marked degenerative changes in the myelin sheath, and especially those in the inner sheath that distorted the axon, there was little evidence of axonal degeneration. Some

axons, however, contained large numbers of margined mitochondria and others contained small focal aggregates of microtubules.

In contrast to the animals examined by Dahme's group, this cat had substantial degenerative changes in all three funiculi of the spinal cord. Diverse changes were noted—axon demyelination, spheroid formation, Wallerian degeneration, and astrocytic scarring. Axonal degeneration appeared to be more prevalent in the spinal cord funiculi than in the cranial or peripheral nerves. Whereas some axonal changes extended into the medulla oblongata, the caudal cerebellar peduncles, and the accessory cuneate nucleus, there was little evidence of degeneration in the brain rostral to this point.

The seemingly disparate pathological changes in the peripheral nerves and spinal funiculi are difficult to explain in the context of a single disease. Nevertheless, it seems very unlikely that separate disorders concurrently affected CNS and PNS.

References are on page 491.

FOCAL TRIGEMINAL HYPERTROPHIC NEUROPATHY IN A HORSE

A prominent onion bulb neuropathy occurred as a secondary finding in the trigeminal nerve and ganglion of a 3-year-old quarterhorse with a 2-month history of recurrent generalized seizures.¹ The seizures in this horse were referable to Sturge-Weber type cerebral changes that included meningocerebral hemangiomatosis and cerebrocortical dysplasia and atrophy.

The left trigeminal nerve and ganglion contained multiple fascicles with onion bulb formations, many of which contained a central axon. The satellite cells in the onion bulbs were strongly positive on immunohistochemical preparations for S-100 antigen as were the Schwann cells of unaffected nerve fibers. At the ultrastructural level, the bulbs consisted of concentric arrays of elongate satellite cells with closely applied basal laminae. In many onion bulbs, a myelinated and often atrophic axon formed the central axis. In some bulb configurations, however, the central axon was lost. In these, the usual place of the axon was sometimes occupied by a Schwann cell profile with or without a collagen pocket.

The relationship of the trigeminal nerve changes and the leptomeningeal hemangiomatosis was unclear. The focal hypertrophic changes in the trigeminal nerve bore some resemblance to cases of human hypertrophic mononeuropathy. This human form of localized hypertrophic neuropathy is considered to be neoplastic in origin, a form of perineurioma.^{2,3} The perineurial origin of the satellite cells is supported by immunohistochemical results. In contrast to the onion bulbs in this horse, those in human cases of hypertrophic mononeuropathy may not be immunoreactive for S-100, a Schwann cell-associated antigen.⁴

References are on page 491.

CONGENITAL HYPOMYELINATING POLYNEUROPATHY IN GOLDEN RETRIEVERS

Hypomyelination of the peripheral nerves has been reported in **Golden Retriever** littermates.^{1,2} Signs of hind limb ataxia appeared around 7 weeks of age. The pups had a crouched stance with mild hind limb weakness and atrophy. At the walk, the hind limbs were circumducted, and at the run a bunny-hopping gait developed. Postural reactions were depressed in the hind limbs. Motor nerve conduction velocities were markedly reduced in sciatic, tibial, and ulnar nerves. Electromyographic recordings, however, revealed few denervation potentials. On study of serial peripheral nerve biopsies from two affected pups, it was found that the number of myelinated fibers was reduced relative to controls, and most myelin sheaths were too thin for the axon caliber. The overall density of axons in the affected nerves was less than normal. Electron microscopy disclosed that the myelin lamellae were fewer than in controls. Schwann cell numbers were increased. In some myelin sheaths, aberrant incisures and poorly compacted lamellae were noted. Macrophages and Büngner's bands were rare, and onion bulbs were absent. Morphometric analysis of the relationship between myelin lamellae and axon circumference in the affected and control dogs indicated that axons of all calibers were hypomyelinated in the Golden Retriever pups. A defect in Schwann cell function was suspected.

In contrast to the inherited hypertrophic neuropathy in Tibetan Mastiffs, there was little evidence of myelin breakdown, macrophage activity, or remyelination in the Golden Retrievers. Braund and colleagues¹ noted, however, that this hypomyelinating condition had features in common with the Trembler mouse. Yet in the Trembler mutant, the dominantly inherited defect has been characterized by demyelination and onion bulb formation.^{3,4} Analysis of lipids in the developing myelin sheaths of the Trembler mouse indicate that the mutation induces a dysmyelination that eventuates in demyelination.^{5,6} It would seem that the deficient myelin in the Trembler mouse is less stable than that in the hypomyelinating retrievers because there is much evidence of demyelination in the former but virtually none in the latter.

There seem to be certain similarities between the Golden Retriever neuropathy and a rare congenital disorder of peripheral myelination associated with arthrogryposis multiplex in human infants.⁷ The latter is thought to result from an arrest of myelination at the promyelin stage.

Braund and others have described a 2-month-old **lamb** with a congenital hypomyelinating neuropathy.⁸

References are on page 491.

HEREDITARY POLYNEUROPATHY IN ALASKAN MALAMUTES

This polyneuropathy, which appears to be transmitted as an autosomal recessive trait in **Malamutes**, was first identified in Norway in 1979.^{1,2} Although signs have been dis-

cerned as early as 7 months, later recognition of the onset at 12 to 18 months is usual. This disorder is characterized by slowly progressive weakness, coughing, and vomiting. Exercise intolerance was evident, as affected dogs required rest and panted heavily after brief periods of walking or running. These dogs also experienced difficulty going up stairs. Muscle strength was diminished more in the hind limbs than the forelimbs. Atrophy was especially conspicuous in the thigh and shoulder muscles. The patellar reflex was depressed or lost bilaterally. Vomiting was correlated with radiographic demonstrations of esophageal dilation. Electromyography revealed denervation potentials, and motor nerve conduction delays were recorded. If recumbent dogs were not euthanized, some improvement usually occurred spontaneously after several weeks, and dogs regained the ability to walk. Subsequent deterioration, in the form of recurrent paralysis or chronic coughing or vomiting, was common.

At necropsy, skeletal muscle atrophy was pronounced in the hind limbs and over the back. Microscopic studies revealed grouped fiber atrophy in most sections, and on histochemical preparations there was fiber type grouping. In several dogs, laryngeal muscle atrophy was marked; prominent megaesophagus was found in all animals. Peripheral nerve fiber degeneration was demonstrable at all levels from the spinal roots to the intramuscular nerves. There was diminished myelin staining and increased endoneurial collagen in some nerves. At the EM level, there was evidence of demyelination, remyelination, and nerve fiber degeneration. Varying numbers of myelin sheaths were undergoing splitting and fragmentation, especially within the inner lamellae. Fragments of degenerated myelin appeared between the axon and the remaining lamellae, as well as in Schwann cells and macrophages. Axons swollen by accumulations of neurofilaments and membranous material were not uncommon.

The pathogenetic mechanisms underlying this inherited neuropathy remain to be defined. The lesions in these Malamutes resembled those described in the hypertrophic neuropathy of Tibetan Mastiff dogs and differed from those in the progressive axonopathy of Boxer dogs and the giant axonal neuropathy of German Shepherds.

We have seen a similar disorder in three young **Beagle-Basset** pups that were diagnosed at 14 weeks with megaesophagus and aspiration pneumonia. The three were from a litter of four with an unaffected female. One pup was referred to this hospital for evaluation. Radiographic examination confirmed the megaesophagus, and neurological examination demonstrated generalized weakness and diffuse muscle atrophy that was worse proximally. Patellar reflexes were lost bilaterally. Electrical studies disclosed widespread denervation potentials including the facial muscles and the muscles of mastication; motor nerve conduction velocities also were decreased.

Postmortem studies indicated widespread radiculoneu-

ropathy. Demyelinating changes were most striking, and these were usually evidenced by the formation of primitive onion bulbs around demyelinated or thinly myelinated axons. Partially demyelinated axons were also noted, with aberrant terminal loop formations. Büngner's bands, which were seen less often, supported the EMG indications of axonal degeneration. Endoneurial collagen was much increased. Whereas the neuropathy in this Beagle had pathological features in common with the hypertrophic neuropathy in Tibetan Mastiffs, the overall clinical and pathological assessments seemed more like those described in the Alaskan Malamutes.

References are on page 491.

HEREDITARY SENSORY NEUROPATHY IN POINTER DOGS

Acral mutilation and insensitivity to pain were first recorded in **shorthaired Pointer dogs** in Czechoslovakia.^{1,2} This condition, originally called toe or paw necrosis, was identified in approximately 100 pups between 1961 and 1974. Analyses of the pedigrees of 26 affected pups by Sanda and Pivnik indicated a recessively inherited condition.¹ Although signs usually appeared in pups of both sexes around 4 months, the age at onset varied from 2 to 12 months. Initially, pups licked slightly swollen, reddened paws and then began to bite their digits. Autoamputation of the digits and superimposed infections followed in paws that were insensitive to a variety of painful stimuli. According to Pivnik,³ Broz and co-workers later identified this disease as hereditary neurotropic osteopathy and described vacuolar degeneration of the glial cells and nerve fibers in the spinal white matter. They reported pronounced demyelination in the ventral, lateral, and dorsal funiculi along the entire length of spinal cord. There was also severe degeneration of ganglion cells and nerve fibers, especially in the dorsal horns and the roots of the cauda equina and in peripheral nerves. Pivnik³ later found the funicular degeneration described by Broz and others in only 1 of 10 affected pups and indicated that in future studies lesions were more likely to be found in the spinal roots, ganglia, peripheral nerves, nerve endings, and vessels of the affected limbs.

More recently, a similar automutilating disorder has been seen in Pointer dogs in North America, and the incidence and geographical distribution have been increasing. Affected pointers have appeared in families of show dogs, quail-hunting strains, and pups from a research breeding colony. Some pups began licking and biting their paws at 3 months; in others, signs of automutilation did not appear until 6 months or later. Progressive acral changes included swollen erythematous paws, paronychia, nail loss, digital and metapodial pad ulceration, digit amputation, fractures, and osteomyelitis. Affected pups were usually unrelenting in their efforts to bite and mutilate their paws, and muzzles and heavy bandages were necessary forms of restraint. As in the Czechoslovakian pointers, the mutilated and fractured

paws were analgesic. Dogs with these extreme acral changes walked and even ran without evidence of lameness or discomfort. The proximal extent of analgesia in the limbs was difficult to define as it faded proximally into an ill-defined area of hypalgesia. Infection of the self-inflicted wounds was associated with prominent lymphadenopathy and leukocytosis.

In accordance with the neurological findings, the pathological changes involved the primary sensory neurons. Macroscopically, there was a distinct reduction in the size of the spinal ganglia and a more subtle thinning of the dorsal roots of the spinal intumescences. Within the ganglia, neuron numbers were reduced when compared to controls, and cell bodies were loosely arranged in thinned ganglionic mantles.^{4,5} Evidence of degeneration of sensory neurons (e.g., chromatolysis or vacuolation) was infrequent; whereas focal proliferations of satellite cells (i.e., Nageotte nodules) formed at sites of cell body loss, were not abundant. In the sensory roots and peripheral nerves, there was degeneration of both myelinated and unmyelinated axons and increased endoneurial collagen. Degenerating myelinated axons were found occasionally, but compact bands of proliferated Schwann cells (i.e., Büngner's bands) more commonly marked the sites of earlier loss of myelinated fibers (Fig. 7-25, A). The latter were of much greater diameter and more regular outline than the small aggregates of axon-depleted Schwann cell processes that marked the sites of unmyelinated fiber loss. Although these Schwann cell processes varied widely in their transected profiles, many had layered or spidery outlines. In some aggregates, the sites normally occupied by unmyelinated axons were filled instead with small bundles of longitudinally directed collagenous fibrils. These collagen pockets were present in large numbers and provided additional evidence of unmyelinated fiber degeneration. Ongoing degeneration of unmyelinated fibers was indicated by lysis of neurotubules and filaments and by variably prominent axonal accumulation of vacuoles and dense bodies (Fig. 7-25, B). There was very little evidence of regenerative sprouting of axons in the wake of the myelinated and unmyelinated fiber degeneration.

In the spinal cord, there was a reduction in myelinated and unmyelinated fiber density and astrocytic scarring in the dorsolateral fasciculus or Lissauer's tract, a tract conveying pain and temperature fibers from the lateral division of the dorsal roots.⁶ However, the medial divisions of the dorsal roots and the dorsal funiculus, paths conveying larger proprioceptive fibers, appeared intact. Nauta-Gygax suppressive silver staining revealed fragmented axons scattered in the dorsal horns. Immunocytochemical demonstrations of **substance P**, a mediator of nociceptive impulses at the central synapses of primary sensory neurons,^{7,9} revealed reductions in this undecapeptide in affected Pointers. Reductions were most striking in the superficial laminae of dorsal horns, that is, the marginal zone and the substantia gelatinosa.¹⁰ In one dog, greater loss of substance P immuno-

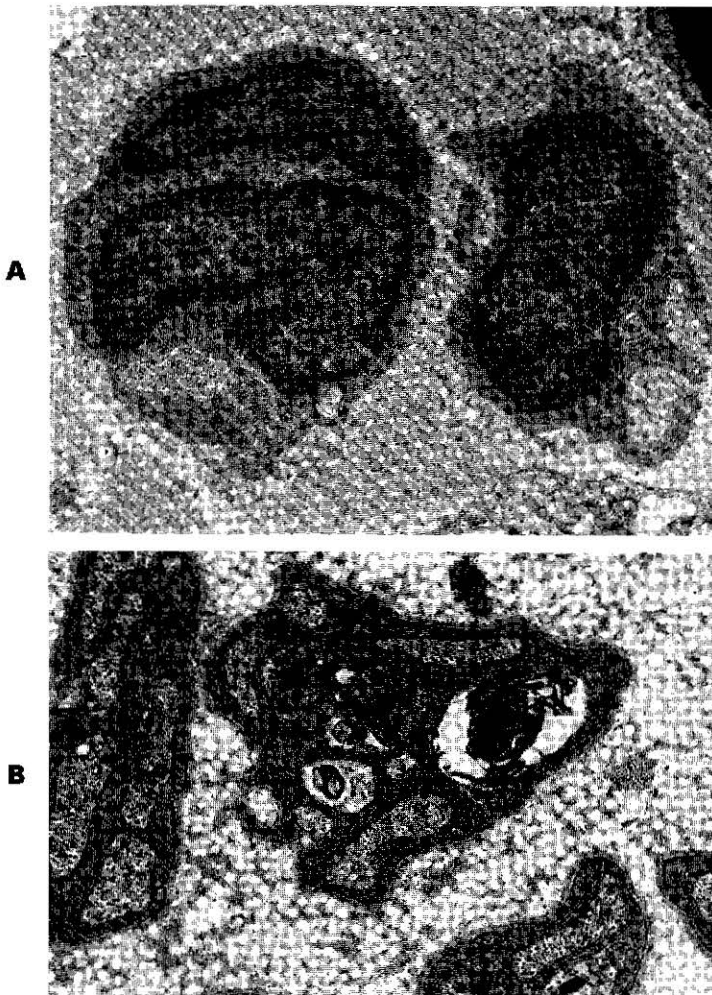


Fig. 7-25. Hereditary sensory neuropathy, dog. A, Büngner's bands, collagen pockets ($\times 19,500$.) B, Degeneration of unmyelinated axons. ($\times 20,455$.)

reactivity was observed in the medial part of the lumbar dorsal horns. This differential reduction was in accord with the demonstrated somatotropic termination of appendicular afferents in this region.¹¹

As the detected amount of neuronal degeneration appeared inadequate to account for the greatly diminished numbers of ganglionic cell bodies, the deficiency was ascribed to insufficient development of primary sensory neurons, followed by progressive postnatal degeneration. The clinical, histological, and immunocytochemical findings indicated a dissociative sensory neuropathy with selective or preponderant involvement of nociceptive neurons—those small, ganglionic cell bodies classically associated with small myelinated or A δ fibers and unmyelinated or C fibers. Such selective involvement, however, was difficult to reconcile with a demonstrated increase in small cell bodies in small spinal ganglia with reduced total cell body counts. This paradoxical increase in small cell bodies, however, may

reflect a more generalized sensory neuron atrophy or growth defect.

In affected Pointers, the attempts to mutilate the acral parts of the extremities persisted even in adults when restraining devices were removed. The basis for these enduring attempts to mutilate analgesic paws remains a matter for speculation. This behavior may reflect a denervation hypersensitivity to substance P at second-order neurons in spinal nociceptive pathways. This possibility receives some support in autoradiographic demonstrations of increased density of substance P receptors in the dorsal horns after destruction of primary sensory neurons in the spinal ganglia of rodents.¹²

Although this canine neuropathy had features in common with the five forms of **hereditary sensory neuropathy** reported in **humans**,¹³ it contrasted with each in certain clinicopathological findings. Of the identified types in humans, the Pointer neuropathy seemed most like type V, in which there is selective loss of pain perception in the extremities.^{14,15} Although this canine disease did not exactly duplicate any of the human sensory neuropathies, it may have value as a model for studies on the pathogenesis of the dysesthesias and automutilation, as well as providing a means to evaluate therapeutic procedures.

References are on page 491.

SENSORY NEUROPATHY IN LONGHAIRED DACHSHUNDS

This sensory neuropathy was thought to be inherited as a simple autosomal recessive trait. In addition to the three dogs that have been evaluated clinically and pathologically,¹⁻⁴ affected individuals were identified in additional litters of **longhaired Dachshunds** in the United Kingdom. Verification of the proposed mode of inheritance, however, has been difficult, as no affected animals presently exist and heterozygous animals have not been identified for breeding studies.

Signs of hind limb ataxia and urinary incontinence appeared in pups soon after birth, but thorough neurological evaluations were not performed until affected dogs were 1.5 years of age. At that time, there were widespread proprioceptive and nociceptive deficits. Self-mutilation in the genital area was noted in one dog. Urinary incontinence and alimentary disturbances were attributed to autonomic nervous involvement.

The most striking pathological changes were found in cutaneous nerves (e.g., saphenous nerve) and the vagus, where an obvious reduction in myelinated axons was accompanied by a large increase in endoneurial collagen. Many of the remaining myelinated fibers contained greatly increased numbers of axonal organelles, but few of these fibers were degenerating. Degenerative changes appeared often, however, in unmyelinated axons. Some affected unmyelinated fibers were marked by increased axoplasmic darkening. Others contained and were often swollen by pro-

liferations of neurotubules and/or vesiculotubular profiles or by formations of multilamellar whorls and stacks. The endoneurium contained many Schwann cell profiles that were devoid of axons. Some of these were typical B  ngner's bands, yet others were very small, consisting of one or two flattened leaflets of Schwann cell cytoplasm. Collagen pockets were described as abundant in the Schwann cells ensheathing unmyelinated axons.

Axonal degeneration was also observed centrally in the dorsal funiculus of the spinal cord. In both the periperal and central projections of the primary sensory neurons, the axon degeneration was most severe distally—in the distal branches of the peripheral nerves and in the cervical portion of the fasciculus gracilis. No changes were encountered at the level of the spinal ganglia or dorsal roots. The distribution of changes suggested strongly that the pathological process should be classified as distal axonopathy. The paranodal demyelination found on teased peripheral nerve preparations was considered to occur secondary to the distal degeneration of axons.

The loss of large (A ) and small (A ) myelinated axons was associated with deficits in proprioception and nociception, respectively. The degeneration of unmyelinated or C fibers was related clinically to analgesia as well as to the autonomic deficits, such as urinary and fecal incontinence. Despite some similarities, this canine disorder did not duplicate any of the human inherited sensory-autonomic neuropathies.

A similar neuropathy has been reported in a 6-year-old **Jack Russell terrier** with abnormal hind limb posture from birth.⁵ In this progressive disorder, severe hind limb proprioceptive and nociceptive deficits were also accompanied by persistent dribbling of urine after micturition. A superficial peroneal nerve biopsy in this case revealed an absence of myelinated fibers and increased endoneurial collagen. Unlike the Dachshunds, however, the unmyelinated fibers were preserved.

References are on page 491.

CANINE GIANT AXONAL NEUROPATHY

This inherited neuropathy has been described in **German Shepherd dogs**, but to date the reported incidence remains very low.^{1,2} Signs of hind limb weakness and ataxia appeared at approximately 15 months. Affected dogs may have an unusual, curly hair coat. Signs progress to include loss of patellar reflexes and placing reactions, atrophy of the distal musculature, and blunted pain sensation. Although the forelimbs seemed to be spared, additional impairments included dysphonia, megaesophagus, and fecal incontinence. Electrical findings included denervation potentials in the hind limbs distal to the stifles and in the forelimb interosseous muscles. Motor nerve conduction velocities in the sciatic and ulnar nerves were slowed, and evoked muscle potentials were reduced and dispersed.

Large swellings appeared distally in the long axons of

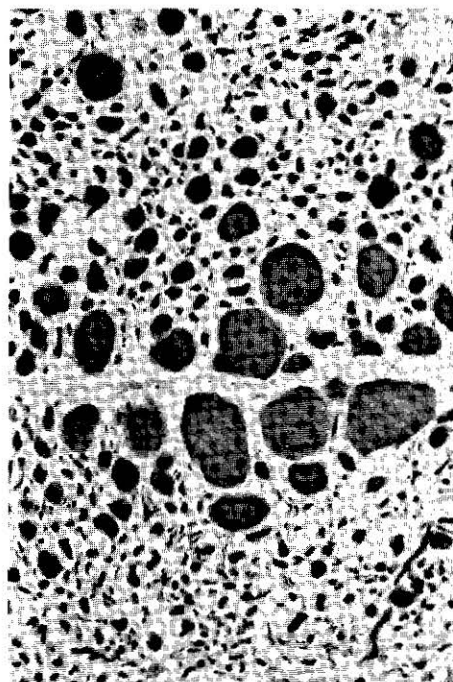


Fig. 7-26. Canine giant axonal neuropathy. Massively swollen axons in fasciculus gracilis of medulla. (Silver, $\times 560$.)

both the peripheral and central nervous system. In the PNS, the distal portions of the tibial, peroneal, ulnar, and recurrent laryngeal nerves contained giant myelinated and unmyelinated axons. Myenteric and sympathetic axons were also affected. In the CNS (Fig. 7-26), swellings also appeared in the distal trajectories of long axons. For example, in the spinal cord, swellings in the fasciculus gracilis and dorsal spinocerebellar tract were most abundant in the cranial cervical segments.^{3,4}

Teased peripheral nerves revealed that the axonal swellings were multifocal, commonly paranodal, and often had a greatly attenuated myelin covering. This focal thinning probably was caused by slippage of myelin lamellae or retraction of the terminal loops from the nodes. There was also evidence of paranodal and segmental demyelination unassociated with local swellings. Ultrastructural study revealed that the swellings contain dense arrays of whorled 10-nm neurofilaments. Excess neurofilaments were also found in axons that do not appear to be enlarged. In affected distal nerve trunks, there was evidence of axon loss. Here, there was a discernible reduction in the number of myelinated fibers, ongoing axonal degeneration, and formation of B  ngner's bands.

The nature and distribution of the changes in canine giant axon neuropathy resembled those induced by various neurotoxins, including acrylamide, IDPN, n-hexane, and methyl-n-butyl ketone. The neurofilamentous accumulations were strikingly similar to those that characterize giant axonal neuropathy in children. The latter is a recessive de-

fect that manifests with peripheral and central nervous signs during the first decade in children who present with abnormal kinky hair.^{5,6} In both children and dogs, the findings fit a distal axonopathy and suggest a metabolic defect that eventuates in impaired axon transport.³ The concurrent proliferation of filaments in other cells (e.g., Schwann cells, endothelial cells, endoneurial fibroblasts) in affected children, however, suggests a more generalized disorder of 10-nm filaments.^{7,8}

References are on page 491.

PROGRESSIVE AXONOPATHY OF BOXER DOGS

This progressive axonopathy has been identified as an autosomal recessive trait in **Boxer dogs**. It has been characterized by widespread lesions in both the central and peripheral nervous systems.

Hind limb ataxia has signaled the onset, usually at 2 to 3 months of age. Ataxia marked by swaying and hypermetria in the hind limbs was slowly or intermittently progressive and often extended later to the forelimbs. Hypotonia with minimal muscle atrophy and patellar areflexia were seen early. Proprioceptive deficits developed more gradually. Electrodiagnostic studies revealed delayed motor nerve conduction velocities and some reduction and temporal dispersion of the evoked muscle potentials.¹⁻⁴ Sensory nerve action potentials were diminished and eventually absent. Spontaneous potentials, indicative of skeletal muscle denervation, were a minor and late-developing feature of this disease. Ocular tremors and head bobbing, which reflected cerebellar involvement, were seen in a few dogs.³

Because clinical signs appear early, it has been suspected that pathological changes may be present at birth or in utero.⁵

The changes in the PNS varied from proximal to distal. Axon swellings occurred paranodally in the extradural spinal nerve roots, most consistently in the lumbar region.⁶ These root axon swellings occurred in the proximal paranodal areas and were frequently associated with attenuation or loss of the myelin sheath.⁷ Affected axons, which increased in frequency with age, contained accumulations of vesicles and vesiculotubular profiles in the subaxolemmal areas and disorganized cytoskeletal elements, especially neurofilaments. As the disease progressed, more axons presented with short internodes and thin myelin sheaths—changes that indicated extensive remyelination in the wake of paranodal myelin loss.⁸ The cervical spinal roots differed from those of the lumbar segments in having numerous clusters of regenerating axons.

In the peripheral nerves, as opposed to the roots, the larger diameter fibers failed to develop the expected caliber. As the disease progressed, evidence of both axon degeneration and regeneration increased in the peripheral nerves.⁶ The high incidence of proximal axon swelling, together with distal axon hypoplasia, suggested impaired transport of neurofilaments. The neurofilaments, which often appeared in disarray in proximal axons, are the major determinants of

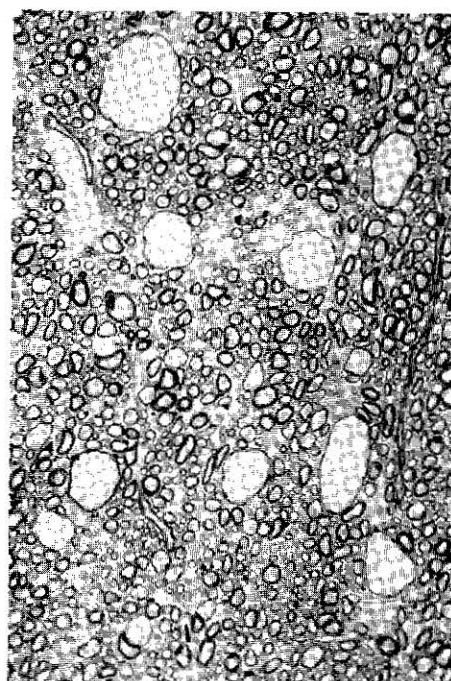


Fig. 7-27. Boxer axonopathy. Swollen myelinated axons in caudal cerebellar peduncle. (Toluidine blue 1-micron section, $\times 560$.)

radial axon growth. A defect in the transport of neurofilaments in a growing animal would be expected to result in distal axon hypoplasia. The myelin sheath changes, based on their spatial and temporal distributions, appeared to occur secondary to fluctuations in axonal size.⁸ The latter assertion was supported when Schwann cells (in nerve xenographs from affected Boxers to athymic mice) failed to reproduce the myelin lesions seen in the spontaneous disease.⁸

In the CNS, axonal swelling and degeneration were especially prominent in the lateral and ventral funiculi of the spinal cord. Axonal spheroids with varying contents (e.g., disorganized neurofilaments, branched vesiculotubular profiles, and mitochondria) appeared in several nuclei and tracts in the caudal brain stem, in the cerebellar white matter (Fig. 7-27) and nuclei, and in the retinal projections.⁹

References are on page 492.

POLYNEUROPATHY IN ROTTWEILER DOGS

This breed-specific disorder¹ was distinguished from the neuroaxonal dystrophy² and the motor neuron disease³ previously described in **Rottweilers**. Braund and associates¹ reported that this disorder, which they observed in eight mature Rottweilers, was characterized by paraparesis that progressed to tetraparesis, spinal hyperreflexia, hypotonia, and appendicular muscle wasting. Electrodiagnostic testing revealed denervation potentials largely in the limb muscles and delayed motor nerve conduction velocity.

Neurogenic muscle atrophy resulted from a neuropathy that was dominated by axonal necrosis that selectively in-

volved the distal parts of long and large diameter nerve fibers. This distal sensorimotor neuropathy was regarded as a "dying back" neuropathy in which the degenerative process spread proximally with time. In the peripheral nerves, the degenerating axons often had a watery appearance with loss of neurofilaments and tubules; other axons contained myelin-like membranous profiles.

The demyelination that was also observed in the peripheral nerves of these dogs was thought to be secondary to axonal degeneration. Similarities were noted between this familial canine neuropathy and hereditary motor and sensory neuropathy (HMSN) type II in people.

We also have studied a polyneuropathy—more specifically, an axonopathy—in one Rottweiler pup. In some ways this axonopathy resembled that reported previously in Boxer dogs. The affected pup was 1 of 2 in a litter of 11 that shortly after birth trembled whenever it stood or walked. By 6 months of age, hind limb weakness was clearly evident, as the dog collapsed and often was unable to rise. At 7 months the dog was tetraparetic, recumbent, and lacked patellar reflexes. At 8 months, a lumbar spinal root biopsy and muscle biopsy were performed. At 15 months, when paralysis had not abated and muscle atrophy had become striking in the distal muscles of the limbs, the dog was euthanized.

Examination of the muscle biopsy samples taken at 8 months revealed denervation atrophy. Study of the lumbar root biopsy revealed axons that were mildly to markedly swollen by neurofilaments. The swellings were often paranodal. The orientation of the accumulated filaments varied, as many deviated from a longitudinal course. Occasionally, the filaments were distributed unevenly within the axoplasm, where they formed an axial bundle that was surrounded by masses of membranous organelles and inclusions. The root axon profiles that were variously swollen by malorientated filaments often were demyelinated or only thinly myelinated. Macrophages were found along demyelinating axons and in the endoneurium. Supernumerary Schwann cell processes in primitive onion bulbs formed crescentic satellites around the thin sheaths of remyelinating axon profiles. Despite widespread involvement of axons, there was little degeneration in the roots, and Büngner's bands were infrequent.

At autopsy 7 months later, there was more evidence of axon degeneration and regeneration in the lumbar roots. Clusters of regenerating axons were encountered frequently in a thickened and fibrotic endoneurium. There was also evidence of scattered axonal degeneration in the funiculi of the spinal cord. The degeneration was most pronounced distally in the spinocerebellar tracts at the level of the medulla oblongata.

Study of distal peripheral nerves (e.g., the peroneal and tibial) disclosed some atrophic axons as well as considerable evidence of prior axon degeneration. Büngner's bands were common, as were clusters of regenerating axons. As in the

axonopathy of Boxer dogs,⁴ it is tempting to speculate that a defect in axonal transport resulted in the axonal neurofilament accumulations in the roots and that this led to distal axon atrophy and degeneration. The observed myelin changes presumably occurred secondary to the axonal abnormalities. It is problematical if this axonopathy with its proximal neurofilamentous accumulations differs substantially from the distal polyneuropathy described by Braund and others.¹

References are on page 492.

EPIZOOTIC PERONEAL AND TIBIAL NEUROPATHY IN UNWEANED WALKER HOUND PUPS

An epizootic form of pelvic limb monoparesis was observed over a period of 1 year in 40 **Walker Hound pups** produced in 9 litters at a single kennel.¹ Pups developed signs at 2 weeks of age in about half of each litter. The affected limbs lacked postural reactions, were areflexic, and had atrophic muscles. Analgesia was noted except on the medial aspect of the limb and in response to pinching the toe. Tibial-peroneal neuropathy was diagnosed. Most pups were euthanized by 6 weeks as paresis worsened and autotomy of digits occurred.

Postmortem studies on one pup with a left monoparesis revealed that only collagen remained in the distal peroneal nerve. In other ipsilateral nerves, axonal density was reduced, whereas endoneurial collagen was increased. Most remaining axons were small, although a few demyelinated fibers were distended with mitochondria and malorientated filaments. Some axons with thin sheaths seemed to be remyelinating. The observed demyelination was judged to be secondary to distal axon degeneration. This distal axonopathy was thought to be linked to a toxin contained in well water used to prepare a milk replacement given as supplement to unweaned pups.

References are on page 492.

PERIPHERAL NEUROPATHY IN GERMAN SHEPHERD DOGS

A male and two female **German Shepherd littermates** that were reared separately developed an unsteady hind limb gait at 9 years of age.¹ This progressed to forelimb and hind limb weakness and reflex reduction. Muscle atrophy became marked in the hind limbs. Serum levels of lipid, creatine kinase, lactic dehydrogenase, and aspartate aminotransferase were elevated. One dog died with pneumonia; the others were destroyed humanely. Pedigree study revealed that similar clinical defects had developed in the mother and grandmother of these dogs.

On gross examination, the sciatic nerves in two dogs were swollen and fibrotic. Microscopically, lesions were limited to peripheral nerves and skeletal muscles. Sections of forelimb and hind limb nerves contained reduced numbers

of the myelinated axons, and thin myelin sheaths indicated remyelination of many of the remaining axons. Nerve fibers undergoing Wallerian degeneration also were encountered together with clusters of regenerating axons.

Muscles of the hind limbs and back contained both atrophic and hypertrophic fibers, as well as endomysial fibrosis and fat infiltrates. Fiber type grouping indicated reinnervation of denervated muscle. Combined silver and acetylcholinesterase staining revealed multiple arborizations of terminal axons and collateral sprouting, which led to the observed fiber type transformation and grouping.

The observed changes were attributed to a dying-back neuropathy with a familial incidence and relatively late onset. The authors suggest that this disorder resembles human hereditary motor and sensory neuropathy (HMSN) type II in its age at onset and pathological changes. It may be that additional lineage, electrodiagnostic, and pathological studies will support the suggested comparison with HMSN type II, the so-called neural variant of Charcot-Marie-Tooth disease.^{2,3}

References are on page 492.

DISTAL DENERVATING DISEASE

A distal denervating neuropathy has been reported in dogs of various breeds in the United Kingdom.¹ In the initial description, the 10 affected dogs varied in age from 1 to 10 years, and 7 were females. In three of these, the onset of signs was closely associated with estrus. The signs that were typical of lower motor neuron disease developed variously. The progression from the onset to maximal weakness was as short as 1 week in 2 dogs, although in the majority (i.e., six dogs) the progression to peak hypotonic quadriparesis required more than 1 month. Pedal and patellar reflexes were depressed or lost. Considerable wasting of the proximal musculature developed. Cranial nerve involvement occurred in some dogs and was manifest as masticatory muscle atrophy, facial weakness, or voice impairment. Sensory deficits were not detected, and swallowing, respiration, and bladder control remained normal.² Electromyography revealed denervation potentials in the appendicular muscles. Motor nerve conduction velocities were at the lower range of normal or reduced slightly. Evoked muscle potentials, however, were reduced markedly.

In most dogs, paresis regressed spontaneously, and full recovery eventuated 4 to 6 weeks after the peak of the illness. Clinical similarities have been noted among this disease, acute idiopathic polyneuropathy,³ and coonhound paralysis. In the last syndrome, however, the onset has been more abrupt and the progression of paralysis has been notably more rapid.

Pathological changes were discerned in the distal branches of motor nerves. The intramuscular nerve fascicles within wasted muscles were largely depleted of myelinated axons. Study of methylene blue-stained preparations re-

vealed compensatory collateral sprouting of surviving terminal motor axons. The resultant reinnervation of muscle fibers may explain the recovery that usually followed in a matter of weeks. Serial paranodal myelin loss was observed along fibers of some distal peripheral nerves (e.g., the peroneal nerve). These demyelinating changes were thought to represent a secondary response along axons that had degenerated distally. No pathological changes were found in the spinal roots or in the proximal portions of the peripheral nerves.

The etiology of distal denervating disease remains unknown. It is suspected that a toxin, other than that of botulinum, may be responsible.⁴

References are on page 492.

DANCING DOBERMAN DISEASE

This progressive neuromuscular disorder appears in male and female **Doberman Pinschers** between 6 months and 7 years of age.¹ Initially, affected animals develop flexion of one hind limb, but within several months these dogs may alternately flex and extend both hind limbs in a dance-like fashion. With time, the gastrocnemius muscles atrophy, hind limb reflexes become hyperactive, proprioceptive deficits develop, and mild weakness eventuates. Tetraparesis developed in a case of 5 years' duration. Electromyography revealed positive-sharp waves, bizarre high frequency discharges, and fibrillations. Microscopic examination of atrophic hind limb muscles has revealed changes described as primarily myopathic, that is, muscle fiber atrophy, hypertrophy, necrosis, and type grouping. Nevertheless, neuropathological changes have also been noted in two necropsied dogs. In one, examination of selected cranial and peripheral nerves revealed changes that were consistent with a distal axonopathy. In the second, however, mild neuronal degeneration and gliosis were detected in the spinal gray matter of L4-L5 and this was accompanied by mild axon degeneration in the spinal white matter and the L6-S1 spinal nerve roots. Although the typical clinical course has been defined for dancing Doberman disease, the pathology, pathophysiology, and etiology remain unclear.¹

References are on page 492.

PERIPHERAL NEUROPATHY IN TWIN CALVES

Recently, a peripheral neuropathy has been identified in twin **Holstein calves** that were 5 and 6 months old.¹ Clinically, signs of progressive muscle weakness predominated. At necropsy, symmetrical neurogenic atrophy as well as fiber hypertrophy were more prevalent in distal than proximal muscles. Axon degeneration which was not encountered at the level of spinal roots appeared distally in both fore and hind limb nerves. This neuropathy was presumed to be a distal axonopathy. The authors could not exclude a toxic or genetic etiology.

References are on page 492.

IDIOPATHIC FACIAL PARALYSIS IN THE DOG AND CAT

This form of facial paralysis in mature animals has occurred exclusive of recognized causes, such as trauma, neoplasms, or otitis media-interna. The onset is typically sudden, and the course variable.¹ In a statistical study of 95 reports of facial paralysis in dogs (79 cases) and cats (16 cases), 74% of the canine and 25% of the feline cases were identified as idiopathic.² Signs of facial paresis or paralysis may be unilateral or bilateral. Facial weakness that was initially unilateral later became bilateral in some dogs.³ Signs include drooping ears, drooling from the corner of the mouth, lip weakness, slight widening of palpebral fissure, and weak or absent palpebral and corneal reflexes.¹ If the weakness is unilateral, the philtrum may be deviated slightly toward the sound side. Electromyographic studies of the facial muscles performed in several cases revealed evidence of denervation in the form of fibrillations.³ Despite the absence of a confirmed association with otitis media-interna, animals with idiopathic facial weakness frequently have had vestibular signs.^{2,3} Moreover, an association with hypothyroidism has been noted in some affected dogs.

Studies of facial nerve biopsy specimens have revealed Wallerian-type degeneration and substantial reduction in the numbers of myelinated axons.^{3,4} Although macrophages with myelin degradation products were abundant in these specimens, inflammatory cell infiltrates were not encountered. Profuse collateral sprouting of axons was reported in one study,⁴ but one documenting electron micrograph seems to depict groups of normal unmyelinated axons rather than regenerating sprouts. The demonstrations of extensive axon degeneration are in keeping with the clinical courses in those animals with unrelenting paralysis or with slow, partially resolving weakness. Lesions of this type and extent, however, do not conform with cases in which weakness resolves quickly.

Comparison with Bell's palsy (idiopathic facial paralysis in humans) may be appropriate.⁵ This palsy is thought to result from edema and compressive ischemia of the facial nerve in its bony canal. The pathogenetic factors triggering the edema, however, may vary to include temperature, blood supply, hypertension, viral infection, diabetes, or pregnancy.

References are on page 492.

EQUINE LARYNGEAL HEMIPLEGIA

Laryngeal hemiplegia, often referred to as roaring, is a common equine problem in which paralysis of the left cricoarytenoideus dorsalis muscle results in an inability to abduct the arytenoid cartilage and vocal fold, which then partially obstruct the airway on inspiration. Endoscopic examination reveals a diagnostic asymmetry of the glottis. On exercise, inspiratory stridor develops as the airflow vibrates a slack and adducted vocal fold. The resultant dyspnea is associated with marked deterioration in the animal's athletic

performance. In most animals, this deficit results from idiopathic distal degeneration of axons in the **left recurrent laryngeal nerve**. Damage in this nerve leads to atrophy of the intrinsic laryngeal muscles, except the cricothyroideus, which is innervated by the cranial laryngeal nerve.

Certain animals are predisposed to develop laryngeal paralysis.¹ The disease has a high incidence in young, tall horses with long necks. It has been estimated that as many as 5% of Thoroughbreds are affected, and a high incidence has been found in draft breeds, such as Clydesdales and Belgians. Studies of the laryngeal muscles and recurrent nerves of draft horse foals indicate that neuropathological changes in the recurrent laryngeal nerves have an early and perhaps prenatal onset.^{2,3} Although a hereditary basis has long been suspected, an exact mode of inheritance has not been defined, and precise explanations for the high incidence in certain breeds and in males are lacking.

Pathological studies revealing that in affected animals there is neurogenic atrophy of laryngeal muscles also have disclosed similar muscle wasting in horses with no clinical or endoscopic evidence of the disease.⁴⁻⁷ Unanimity is lacking on the extent of denervation necessary to produce clinical evidence of dysfunction.⁸ Although muscle wasting in "roarers" is severe on the left especially and surprisingly in the adducting cricoarytenoideus lateralis muscle,⁹ neurogenic atrophy appears in the right laryngeal muscles as well.

Contemporary studies associate laryngeal hemiplegia with a progressive distal loss of large myelinated fibers.^{6,10-12} The pathological process, called a distal axonopathy, is said to selectively involve the largest axons. Quantitative studies of affected recurrent nerves reveal a progressive proximal to distal loss of myelinated axons^{8,10} with preferential loss of medium-sized and large myelinated axons in the left adductor branch.¹³ The observed amount of active or ongoing axonal degeneration has varied. Evidence of prior degeneration of large axons is abundant in the form of many Büngner's bands, some of which retain ovoids of degenerating myelin (Fig. 7-28, A). Other bands contain regenerating axon sprouts, and in some the component Schwann cells with their regenerating axons separate slightly to form clusters. The distal loss of axons is accompanied by considerable endoneurial fibroplasia.

Duncan and Hammang noted that degenerating axons are often characterized by accumulations of organelles in paranodal outpocketings or in large internodal swellings. The proximal and distal paranodal accumulations of organelles seem to be unique to this equine neuropathy,¹⁴ but the perturbation that produces this unusual change is unknown. The larger internodal accumulations of organelles, however, have been associated with impaired rapid axonal transport.^{15,16}

In contrast to Duncan and Hammang, Cahill and Goulden¹¹ report that the predominant distal change is axonal atrophy rather than axon distension or swelling. Affected axons are of small diameter and encompassed by

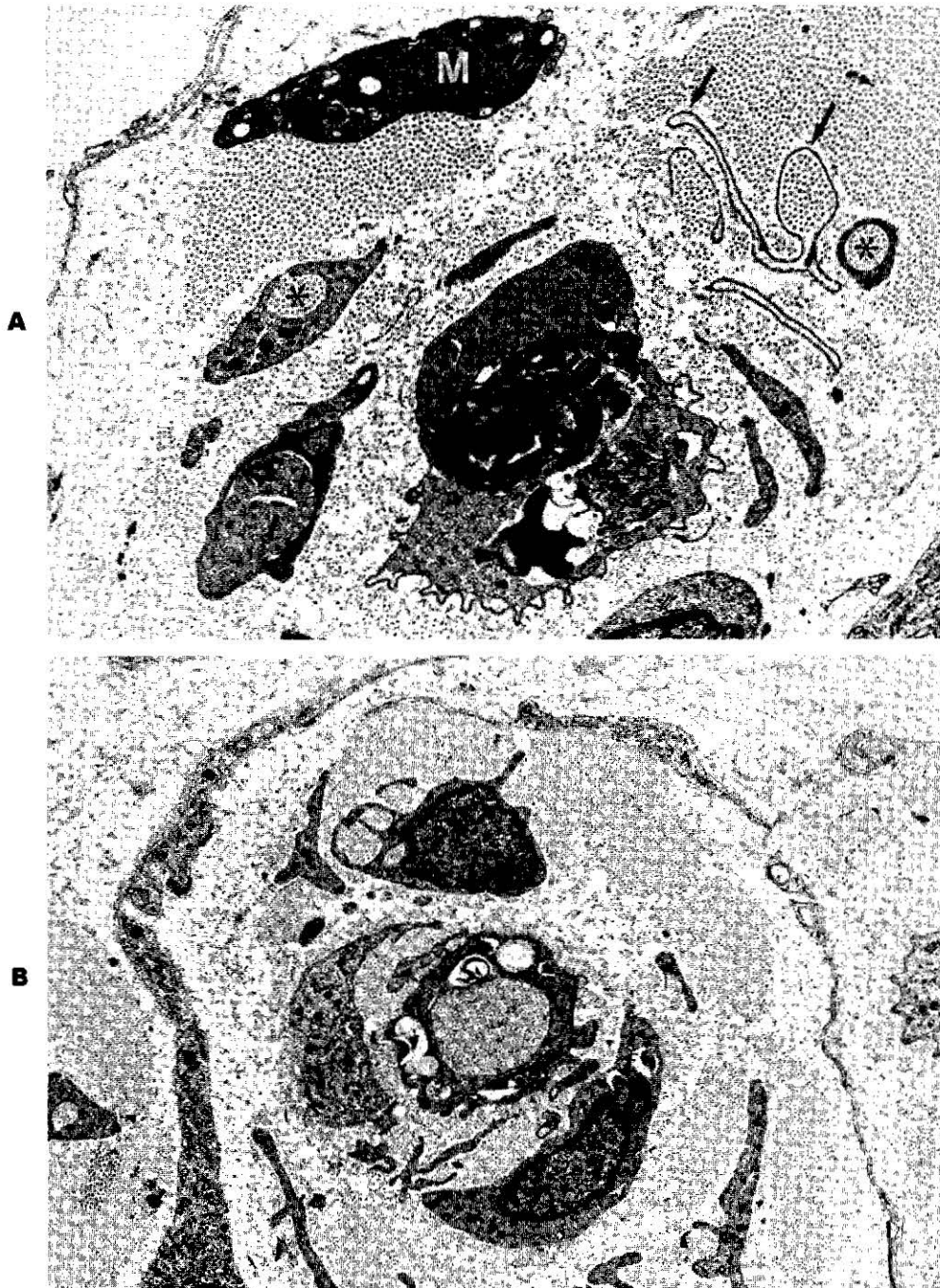


Fig. 7-28. Equine laryngeal hemiplegia. **A**, Following distal axonal degeneration, Büngner's bands with ovoids of degenerating myelin are formed. Note endoneurial fibrosis, macrophage (*M*), remnants of Schwann cell basement membrane (*arrows*), and collagen pockets (*asterisks*). ($\times 12,925$.) **B**, Onion bulb and endoneurial fibrosis. ($\times 8300$.)

disproportionately thick myelin sheaths. Chronic atrophy of distal axons has been associated with a reduced delivery of neurofilaments via slow axonal transport.^{15,16} Despite these pathogenetic distinctions, swollen and atrophic axons may appear concurrently in spontaneous neuronal degenerations,¹⁶ and that seems to include equine laryngeal hemiplegia.

Although prior EM studies stressed the selective involvement of large myelinated fibers, we have found evidence of unmyelinated axon degeneration in the form of multiple collagen pockets in Schwann cells that are depleted of axons and in many small aggregates of flattened Schwann cell processes without axons.

Teased-nerve studies consistently show evidence of

chronic demyelination and remyelination in the presence of many short, thinly myelinated internodes.^{10,12} At the ultrastructural level, these intercalated nodes appear as onion bulbs (Fig. 7-28, B). The demyelination in these recurrent nerves appears to be secondary to primary axonal changes. Such secondary demyelination has been previously associated with axonal atrophy¹⁷ and also with axonal swelling.^{14,18}

Studies by Cahill and co-workers^{8,11,12} and by Kannegieter¹⁹ disclosed that degenerative axonal changes are not restricted to the recurrent or vagus nerves, but involve long peripheral nerves in the hind limbs as well. These studies suggest that laryngeal hemiplegia is the major clinical manifestation of a more widespread peripheral nerve degeneration, that is, a **polyneuropathy**. The disease process causing idiopathic laryngeal hemiplegia also has an effect on distal hind limb nerves and muscles.¹⁹

The precise cause of the neural degeneration in laryngeal hemiplegia has remained elusive.²⁰ Mechanical etiologies have been proffered. These include stretching of the tethered left recurrent nerve with resultant vascular insufficiency²¹ or compression of this nerve at the aortic arch with impaired axon transport.¹⁰ An embryological hypothesis implicates mechanical tension on the left recurrent laryngeal nerve as it, with its turn around the sixth aortic arch, is shifted caudally with the heart during development.²² Recent pathology studies in foals suggest that recurrent laryngeal neuropathy has an early and possibly prenatal onset.^{3,23} This theory anticipates considerable prenatal damage to the nerve. Infectious agents also have been implicated, but their relationship appears tenuous.¹ A role for poisonous plants may require closer scrutiny because in New Zealand outbreaks of laryngeal hemiplegia occur with stringhalt in the late summer or autumn in horses on pastures containing the plant *Hypochaeris radiata*.^{24,25}

Other forms of intoxication include lead and organophosphates, both of which have been occasional causes of laryngeal paralysis. Delayed organophosphate toxicity has resulted in small outbreaks of bilateral laryngeal paralysis. Axon degeneration in these cases is widespread, with changes in peripheral nerves as well as in the spinal cord.^{26,27} The suggested causal role of thiamine deficiency in equine laryngeal paralysis may warrant additional study.²⁸ A thiamine association had been viewed as unlikely because neuropathological changes were limited to the recurrent nerves.¹⁰ However, Cahill and co-workers^{11,12} demonstrated that laryngeal hemiplegia is part of a true polyneuropathy lends credence to an underlying metabolic defect. Cahill and co-workers have speculated less specifically that axonal atrophy results when the axonal demand for depleted substances exceeds the cell body's ability to provide them. Thorough assessment of the cell bodies in this disease will require that they first be precisely localized within nucleus ambiguus in the equine brain stem.

Right laryngeal hemiplegia may also occur as a result of less arcane pathogenesis. Right laryngeal paralysis has been

associated with paravascular injections of the right jugular vein, intracranial abscessation, and mediastinal lymphosarcoma.²⁹ Mediastinal lymphosarcoma has also produced bilateral laryngeal paralysis.

References are on page 492.

CANINE LARYNGEAL PARALYSIS

A hereditary form of laryngeal paralysis in **Bouvier des Flanders** has been studied thoroughly. Typically the onset of clinical signs occurred in young Bouviers between 4 and 6 months of age.¹ Owners generally complained that affected dogs had decreased endurance and noisy breathing.² Exercise produced stridorous respiration and dyspnea. Stress commonly led to hyperthermia, cyanosis, vomiting, and sometimes life-threatening laryngospasm. Laryngoscopy in 105 affected Bouviers revealed bilaterally or unilaterally decreased mobility of the vocal folds. When mobility was preserved unilaterally, it was always on the right. Bilateral electromyographic studies in affected dogs revealed denervation potentials in most cases in several, but not always the same, intrinsic laryngeal muscles.¹ Breeding experiments have established that laryngeal paralysis in Bouviers is inherited as an autosomal dominant trait.³

Studies of biopsy specimens of left dorsal cricoarytenoid muscle in 53 cases revealed changes characteristic of denervation atrophy. Histopathological study of the recurrent laryngeal nerves revealed bilateral evidence of Wallerian degeneration in the form of numerous digestion chambers with axonal fragments. Endoneurial collagen and Schwann cells were increased in these nerves. The axon degeneration occurred over the entire length of the recurrent nerves.¹

The nucleus ambiguus was studied in 20 Bouviers, and neuronal degeneration was found bilaterally. Degenerating cell bodies were described as having less pronounced or smaller Nissl granules and indistinct cell and nuclear membranes. The most pronounced change in the nucleus ambiguus, however, was a distinct reduction in the number of neurons. With this numerical reduction, the length of the nucleus was shortened caudally. Evidence to date indicates that the fiber degeneration along the entire length of the recurrent laryngeal nerves is secondary to degeneration of neuronal cell bodies in the nucleus ambiguus.^{1,2} In a few of the Bouviers with laryngeal paralysis, there was also bilateral denervation of the cranial tibial muscle, a finding that suggests wider involvement of motor neurons in this inborn neurodegeneration.

An inherited laryngeal paralysis has been found in **Siberian Huskies** and **Husky-crossbreed** racing sled dogs. Affected Husky dogs have a similar phenotypic appearance with blue eyes, white faces, and freckles. Unilateral or bilateral disease produced hoarseness and reduced racing performance in these working dogs.⁴

Affected dogs have been studied in consecutive generations of four families.⁵ Electromyography and laryngeal muscle biopsies have provided evidence of denervation, and

in one affected pup gliosis and neuronal atrophy were observed in the vagal nuclei.

Congenital or hereditary laryngeal paralysis also has been observed in young **Dalmatians** as only one sign of a generalized polyneuropathy.^{6,7} Additional clinical manifestations of neurological impairment included megaesophagus, hyporeflexia, limb muscle wasting, fasciculations, limb hyperextension, facial and lingual paralysis, and hypermetria.⁸ Studies of laryngeal and limb muscles and nerves from affected Dalmatians demonstrated that neurogenic muscle atrophy results from necrosis and loss of myelinated nerve fibers. Electrophysiological and pathological studies in these cases have indicated a largely distal distribution of abnormalities. These findings suggested a dying-back neuropathy that may be inherited as an autosomal recessive trait.

Acquired forms of laryngeal paralysis also have been reported in the dog. O'Brien and others⁹ studied 10 dogs in which stridorous respiration progressed to obstructive dyspnea. These dogs were members of large breeds, and St. Bernards were heavily represented. Study of intrinsic laryngeal muscle biopsies taken at the time of corrective surgery disclosed neurogenic atrophy. Samples of the recurrent laryngeal nerves were obtained from four dogs, and these contained degenerative changes: axon and myelin degeneration, axon loss, and endoneurial fibrosis. In one dog, the recurrent laryngeal neuropathy was related to sclerosis of blood vessels throughout the CNS. Gaber and colleagues,¹⁰ Love and associates,¹¹ and La Hue¹² studied large numbers of dogs with acquired laryngeal paralysis and also found a high incidence in large and giant breeds; Labrador Retrievers, St. Bernards, Irish Setters, and Afghan Hounds were commonly affected. Castrated males, in particular, seem to be at risk, and affected animals are usually over 7 years old.¹³ In some of these dogs, clinical, electrical, and/or biopsy evidence of peripheral nerve damage has been presented. The concurrence of recurrent laryngeal and peripheral nerve involvement suggested that laryngeal paralysis, at least in some dogs, may be a manifestation of polyneuropathy.^{6,10} The pathogenesis of the neuropathological changes has not been studied thoroughly. A clinical association has been made between laryngeal paralysis and hypothyroidism in a number of cases,¹⁴ and it has been speculated that a hypothyroid myopathy or neuropathy may be manifest, most notably as laryngoplegia.

Although laryngeal paralysis has been described and treated surgically in three cats, the pathogenesis in these cases was not determined.¹⁵

References are on page 493.

STRINGHALT

Stringhalt, an ancient equine disorder cited in Shakespeare's *Henry VII*, is characterized by an abnormal gait with exaggerated flexion and delayed extension of one or both hind limbs during progression.^{1,2} Two forms of stringhalt have been recognized. There is **true** or **ordinary string-**

halt, which occurs sporadically, usually as a unilateral problem in individual animals, and there is **Australian** or **dandelion stringhalt**, which typically occurs in outbreaks affecting many horses in a confined geographical area and often involves both hind limbs.³ It has been suggested that the differences between ordinary and Australian stringhalt may be arbitrary,⁴ but the circumstances under which they develop and their presentations clearly differ. Australian stringhalt, unlike the ordinary form, develops commonly in late summer or autumn under arid conditions and with ingestion of Australian dandelion or flatweed (*Hypochaeris radicata*), European dandelion (*Taraxacum officinale*), or mallow (*Malva parviflora*).^{4,5} Although speculation has varied widely on etiological factors in true stringhalt, the Australian form rather consistently has been related to ingestion of a plant toxin, perhaps a mycotoxin.^{1,4} Ordinary stringhalt has a worldwide distribution, but outbreaks of dandelion stringhalt have been reported only in Australia, New Zealand, and the western United States.^{1,4,6,7} The possibility exists, however, that this latter form has a wider distribution. For example, bilateral stringhalt was observed simultaneously in the only two horses present on a New York state farm.⁸

The clinical findings in dandelion stringhalt vary in severity: the degree of hind limb flexion, the duration of flexion, and the constancy of this gait abnormality.⁴ Severe cases typically present a bilateral bunny-hopping gait; in a few animals, forelimb involvement may manifest as stumbling or scuffing associated with knuckling at the carpus. Marked muscle atrophy may develop in the hind limbs, and dyspnea or stertorous respiration may reflect concurrent laryngeal hemiplegia.⁴ Occasionally a horse may have difficulty rising.^{1,4} Huntington and others⁵ recorded increased electromyographic activity in the long digital extensor muscles of affected horses, and the conduction velocity in the deep peroneal nerve was substantially reduced. In further contrast to ordinary stringhalt, which may remit only following tenectomy of the lateral digital extensor muscle, spontaneous recovery is usual in the Australian form. Recovery, however, may be protracted.⁹ Electrical studies suggest that enlarged motor units form in recovery as denervated muscle fibers are incorporated into the terminal innervation of intact axons.⁵

Various inciting factors have been suggested for ordinary stringhalt, including articular lesions of the stifle or hock, foot injuries, trauma to the long extensor muscle with subsequent contracture, and a functional disturbance of the stretch reflex.⁴

Studies of Australian stringhalt have provided evidence of peroneal and tibial nerve degeneration and associated neurogenic atrophy of hind limb muscles.^{1-3,10,11} Hind limb muscle fiber atrophy and diffuse fibrosis are most severe in the long and lateral digital extensor, the cranial tibial, gracilis, and deep digital flexor muscles.¹⁰ The observed Wallerian-type degeneration of large myelinated fibers in the

distal branches of the sciatic nerve, which occurs in the absence of any consistent spinal cord change, supports the assertion that Australian stringhalt is a manifestation of a distal axonopathy.^{2,10,12} The clinical concurrence of stringhalt and laryngeal hemiplegia lends additional support to this pathogenesis because the latter disorder reflects a distal degeneration of axons in the left recurrent laryngeal nerve. In this very long nerve, active myelinated fiber degeneration is observed in conjunction with axon atrophy, suggesting a defect in axonal transport.¹³ The occurrence of segmental demyelination and remyelination in the recurrent and peripheral nerves is thought to be secondary to or a consequence of distal axon degeneration.²

At this point, it still seems preferable to regard stringhalt as a clinical sign rather than a disease. In this regard, stringhalt also may be an occasional manifestation of myopathy or spinal cord disease.¹⁴ It has occurred in cases of protozoal myelitis¹⁴ and occasionally in association with longstanding cases of equine motor neuron disease.¹⁵ In the latter, it possibly may be associated with the degeneration and loss of the primary sensory neurons, which also occur in this disease. The complex nosology of stringhalt and equine peripheral nerve disease emerges in a report by Robertson-Smith and associates,¹¹ who described an array of neuropathies that occurred regionally during drought conditions in Australia. These included one case of radial paralysis, two cases of paraparesis with muscle atrophy, and three cases of Australian stringhalt, one of which was severely wasted and unable to walk. In all cases, Wallerian-type degeneration appeared in peripheral nerves and was accompanied by neurogenic muscle atrophy.

References are on page 493.

LEUKOENCEPHALOMYELONEUROPATHY IN BIRMAN CATS

A diffuse neuroaxonal degeneration involving elements of both the CNS and PNS has been observed in **Birman kittens**.^{1,2} Signs appeared at 8 to 10 weeks of age in three female littermates. Posterior ataxia and locomotor deficits were evident, as was hypermetria in all limbs. The kittens stood and walked on their hocks, which were splayed out; they were said to have "calf hocks." All three had proprioceptive deficits and slight muscle atrophy. Electromyographic examination performed on one kitten revealed denervation potentials in the muscles of the hind limbs; motor nerve conduction velocities in the tibial nerves were within normal limits.

Postmortem studies of the CNS revealed a clear loss of myelinated fibers in the cerebellar white matter, the cranial fasciculus gracilis, and the pyramidal tracts, especially in their lumbar trajectory. A notable loss of myelinated and unmyelinated axons was found in the sciatic nerves, but the contributing spinal nerve roots appeared intact. The observed changes suggested a dying-back neuropathy, that is, a central-peripheral distal axonopathy. This degenerative

disorder involving diffusely the white tracts of the CNS and the peripheral nerves was thought to have a hereditary basis.

References are on page 493.

KANGAROO GAIT IN EWES

Kangaroo gait describes a locomotor disorder seen infrequently in lactating ewes of the large breeds in which the affected animals distribute their body weight mostly on the hind limbs; the forelimbs, which are advanced with a high-stepping, hypermetric action, tend to knuckle at the carpi.¹ The animal's gait typically is bounding, as the name implies, with propulsive leaping movements of the hind limbs. Occasionally, the hind limbs are also affected, and this results in a crouched, humpbacked stance and a hobbling incoordinated gait.² This disorder was seen first in New Zealand and later in the United Kingdom. It develops acutely in ewes in lactation and up to 1 month after weaning.³ Complete recovery is usual sometime after lactation. In the initial pathological study of two ewes, Duffell and others¹ found extensive Wallerian degeneration in the radial nerve bilaterally (Fig. 7-29) and in a few fascicles of the brachial plexus. In one of the ewes, lesser amounts of Wallerian degeneration occurred also in the sciatic, tibial, and peroneal nerves. In this study no changes were noted in the spinal cord or brain. Atrophic changes in the forelimb extensor muscles appeared to be neurogenic.

Barlow and Grieg,² in a study of five cases of kangaroo gait described in three an astrocytic-based spongy change in some CNS regions, including the hippocampus, various brain stem nuclei, and the spinal ventral horns. In the PNS a diffuse spinal ganglionopathy was characterized by swelling, proliferation, and palisading of satellite cells without sensory cell body changes, and Wallerian degeneration appeared in the radial nerves. They suggested that reversible ventral horn spongy changes result in more slowly resolving

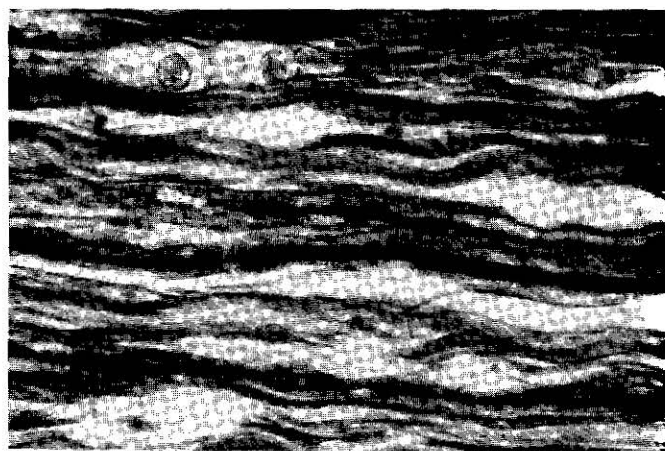


Fig. 7-29. Kangaroo gait, ewe. Wallerian degeneration in the radial nerve. (Luxol fast blue-silver, $\times 560$.)

alterations in the peripheral nerves and consequent muscle atrophy. Later, O'Toole and others³ studied the radial and tibial nerves from two ewes with kangaroo gait of 6 weeks' duration. The radial nerves contained evidence of extensive and longstanding degeneration of myelinated axons in the form of Büngner's bands. Clusters of regenerating axons were also present among the proliferated collagenous fibrils of the endoneurium. These authors suggested that kangaroo gait results from local entrapment or compression of the radial nerve but did not incriminate a specific site. In this regard, the acute onset, preferential involvement of the forelimbs, and axon degeneration are not very different from those found in canine brachial plexus neuropathy or neuritis.

Perhaps kangaroo gait should be regarded as a clinical sign rather than a distinct nosological entity because a similar gait has been observed in 2- to 5-month-old lambs in Kenya that develop an idiopathic focal symmetrical poliomyelomalacia of the cervical spinal cord intumescence.⁴ In these cases, of course, the peripheral nerve degeneration resulted from necrosis of the ventral horn cells, and recovery under these circumstances was precluded.

References are on page 494.

FELINE ISCHEMIC NEUROMYOPATHY

In cats, aortic or iliac arterial embolism usually develops secondary to cardiac disorders (e.g., endomyocarditis, cardiomyopathy) wherein there is thrombus formation and detachment. Occlusion of the caudal aorta or its main branches results in sudden paraparesis or paralysis. Weakness is pronounced distal to the stifle, especially in the cranial tibial muscles.¹⁻³ Affected animals lose the ability to flex or extend the hock. The femoral pulse is lost, and the limbs are cool.

The pedal reflex is absent. Although the gastrocnemius muscles are swollen and painful, nociception is lost in more distal portions of the limbs. The patellar reflexes may be lost, depressed, or intact. Sciatic nerve stimulation may not evoke recordable potentials in distal muscles; if potentials are evoked, they are of very low amplitude. Despite severe initial impairment, a femoral pulse commonly returns, and neuromuscular improvement follows gradually.

Histopathological studies disclose that peripheral nerve changes develop at the level of the middle to lower thigh. Within the sciatic nerve and its branches, degenerative changes are most striking in the central areas of the fascicles. Proximal to the level of ischemic degeneration of axons, nerve fibers commonly undergo paranodal and segmental demyelination. A proportion of the axons in the affected nerves are fully preserved, and others sustain only myelin changes and remain intact through their distal course. The neural changes resulting from spontaneous aortic occlusion are clearly more sparing than the necrosis of all fascicular components that is produced experimentally in the peroneal and tibial nerves of cats with combined aortic and femoral arterial ligations.⁴

Clinical improvement observed within 2 or 3 weeks of onset has been attributed to remyelination of surviving axons. Fuller recovery of neural function occurs in subsequent months through axon regeneration. Muscle alterations vary from infarction with rhabdomyolysis (chiefly in the cranial tibial muscle) to mixtures of myopathic and neurogenic changes in other muscles. The failure to achieve recovery has been ascribed to muscle infarction or recurrence of thromboembolic occlusion.

References are on page 494.

Traumatic lesions of the peripheral nervous system

AVULSIONS OF THE BRACHIAL PLEXUS

Avulsions of the brachial plexus occur in **dogs and cats** as a result of road accidents.¹ In dogs, this traumatic injury is incurred through traction on the forelimb or severe abduction of the scapula.^{2,3} The damage occurs at the level of the spinal roots because they lack a perineurium and so are less resistant to stretch than peripheral nerves.¹ Avulsion of all roots of the plexus (i.e., C6-T1 roots) or caudal avulsions involving the C8 and T1 roots are more common than injuries affecting the cranial roots of the plexus (i.e., C6 and C7).⁴ The C8 root is the one most frequently involved.⁵ For clinical signs to be manifest, roots from at least two spinal segments must be affected.^{5,6} Plexus avulsions are often

diagnosed as radial nerve paralysis.⁷ The observed deficits vary with the extent of root involvement. Total avulsion of the roots of the plexus produce flaccid paralysis of the entire limb with sensory loss distal to the elbow. A partial Horner's syndrome may occur with damage to T1, and there is ipsilateral loss of the motor component of the panniculus or cutaneous trunci reflex as a result of C8 and T1 involvement.^{4,8}

The root avulsions occur intradurally. The root sleeves may persist while the axons within them are disrupted, or both components may be lost. The avulsion can be incomplete, as some attenuated tissue elements persist.¹ In some cases, certain rootlets may be detached while others issuing

from the same spinal segment may survive.⁴ Axon disruption occurs in the roots, at root-spinal cord junction, and within the spinal cord. Griffiths¹ found retraction bulbs on motor axons traversing the ventral funiculus. Neuroma formation commonly occurs on the pial surface of the spinal cord, where the damaged axons emerge at the ventral root exit zone. There may be hemorrhage within the spinal cord. Retrograde chromatolysis is seen in ventral horn cells of the intumescence. In longstanding injuries, the reactive neurons eventually shrink, and their numbers are ultimately reduced. Dorsal root damage is prolonged into the spinal cord as Wallerian degeneration in the fasciculus cuneatus, and avulsion of the ventral roots produces Wallerian degeneration in motor and mixed nerves of the forelimb. The axons of the cutaneous nerves, surprisingly, are often well preserved despite loss of sensation. Their preservation can be explained by intradural avulsions that interrupt the sensory axons proximal to the ganglion, thus leaving the distal axonal projections in continuity with the ganglionic cell bodies. de Lahunta⁹ notes also that sensory preservation occurs in some cases because the dorsal roots survive when ventral roots are avulsed. The sensory roots seem to be less prone to injury.¹

In some cases, the roots may be contused rather than avulsed.⁶ This less severe form of trauma carries a good prognosis, whereas there is no hope of improvement with extensive avulsions because effective regeneration does not occur between the ruptured stumps.⁵ In an electrodiagnostic study of 30 dogs with traumatic brachial plexus syndrome, only 8 were using their limbs satisfactorily 4 or more months after onset.¹⁰

Traumatic injury of the roots of the brachial plexus is also seen in **wild birds** (Fig. 7-30). de Lahunta and others¹¹ examined five birds with unilateral wing paralysis and palpable atrophy of the pectoral muscle mass. In four of these, the spinal nerves that form the plexus were discolored, shrunk, and fibrotic. Microscopic examination of the spi-

nal nerves, plexus components, and peripheral nerves of all birds revealed extensive degeneration of axons and Büngner's band formation. In the spinal cord, interruption of sensory fibers central to the spinal ganglia resulted in Wallerian degeneration in dorsal root entry zone, the dorsolateral fasciculus, and fasciculus cuneatus. On the motor side, microscopic examination indicated detachment of the ventral rootlets from the cervical intumescence. The ventral horns contained chromatolytic cell bodies or, with longer post-traumatic intervals, there was loss of motor neurons and gliotic scarring.

References are on page 494.

CAUDA EQUINA SYNDROME

In this **canine syndrome**, deficits result from damage to the spinal roots forming the cauda equina: the roots emanating from the L7, S1-S3, and Cd1-Cd5 spinal segments.¹ The usual cause of the cauda equina syndrome is lumbosacral stenosis and/or stenosis of the intervertebral foramina. Clinical signs evolve insidiously and vary. The most consistent finding is pain elicited in the region of lumbosacral articulation.²

Indrieri¹ notes that **lumbosacral (L-S) stenosis in small breeds** (e.g., Poodle, Beagle, Lhasa Apso) is similar to human congenital L-S stenosis, where there is a failure of the neural arch to develop to normal dimensions. In these dogs stenosis occurs at the L-S junction and the L6-L7, L7-S1, intervertebral foramina. In 15 cases³ clinical findings included pain elicited over the lumbosacral area; hind limb proprioceptive loss; muscle weakness and wasting in the distribution of the sciatic nerve; paresthesias with self-inflicted lesions of the hind limb, perineum, or tail; and sphincter impairment. Males and females were affected equally, and signs appeared between 3 and 8 years of age.

The more frequently reported **cauda equina syndrome in large breeds** appears comparable to human acquired L-S stenosis, wherein degenerative changes gradually reduce the spinal canal or intervertebral foramina. These changes, which probably develop through cumulative strain on connective tissues, include disk herniation and hypertrophy of ligaments and joint capsules.⁴ More males than females are affected, and the average age at onset is 6 to 7 years.^{1,5} Various large breeds have been affected (e.g., Great Dane, Airedale Terrier, Irish Setter, Labrador and Golden Retrievers), but the prevalence is especially high in **German Shepherds**.^{1,6} In a study of 57 affected dogs by Jaggy and associates,⁵ 45% were German Shepherds. This prevalence suggests a genetic basis for this breed predisposition.⁵ Ness⁸ also reported a predilection in Border Collies. The clinical findings are variable and may be unilateral or bilateral. In addition to lumbosacral pain, there may be hind limb paresis and muscle wasting, fecal and urinary incontinence, and tail and anal weakness. Unlike the condition in small breeds, self-mutilation has not been observed in the acquired L-S stenosis of large breeds. Factors considered in the evolution



Fig. 7-30. Brachial plexus avulsion. Red tail hawk.

of damage to the spinal roots and nerves include the direct effects of pressure, inflammation and swelling, tension, and ischemia.¹ In the German Shepherd, the cauda equina syndrome can be complicated by coxofemoral osteoarthritis and degenerative myelopathy.⁷

Neurological signs comparable to those seen with L-S stenosis can result from subluxations, neoplasms, disk extrusions, or diskospondylitis.² Fractures and luxations resulting from road accidents in dogs and precipitous falls in cats produce acute deficits that vary in severity and duration, depending on the site and nature of damage to the cauda equina. Whereas traction and shearing forces may cause neurotmesis in the form of root or spinal nerve avulsion, this permanent type of damage is initially difficult to distinguish clinically from neuropraxia caused by extraneural or neural swelling.¹ The prognostic distinction between these two types of lesions can be made by exploratory laminectomy or by providing adequate time for spontaneous recovery.

References are on page 494.

INJECTION INJURIES TO PERIPHERAL NERVES

Iatrogenic nerve damage by injections may result from (1) needle puncture, (2) the drug deposited, (3) pressure from a hematoma, or (4) scarring around the nerve. Various combinations of the above may contribute to the injury.¹ In domestic animals, the sciatic nerve is most commonly damaged by deep intramuscular injections. Young animals are at increased risk because of lesser masses of muscle. It has been found that sciatic nerve damage occurs in calves and less frequently in dairy cows receiving multiple injections or injections of irritating materials, particularly tetracycline or vitamins in the gluteal muscles.^{2,3} Injections in the gluteal muscles of cattle are commonly given by lay persons who may be reluctant to admit they have treated their animals. Similarly, iron-dextran injections into the gluteal muscles of young pigs also may result in sciatic nerve damage. Injections deep into the caudal thigh muscles may also damage the sciatic nerve in dogs and cats⁴ and neonatal calves.²

Experimental studies of injection injuries in rats have revealed that intrafascicular injection was invariably associated with severe nerve damage, whereas epineurial or extrafascicular injections usually produced minimal damage. Intrafascicular injections produced axon and myelin degeneration in the injected fascicles^{5,6} and retrograde chromatolytic changes in the spinal ganglia and ventral horn cells. The severity of the damage varies with the drug and dose administered.^{5,6} Certain drugs have greater potential for causing neural damage. Penicillin, diazepam, and chlorpromazine cause widespread axonal degeneration after intrafascicular injection. A moderate degree of damage occurs after intrafascicular injection of chloramphenicol, gentamicin, iron-dextran, and cephalothin. With the latter substances, there is total degeneration of myelinated axons, but relative sparing of unmyelinated axons. Local disruption of

the blood-nerve barrier and the resultant endoneurial edema and increased pressure are thought to contribute significantly to intrafascicular injection injuries.^{5,6}

In the preceding experimental studies, there was substantial evidence of regenerating axon sprouts in the injected sciatic nerves, and full functional recovery was observed after 12 weeks. Similar rapid and complete recovery, however, should not be anticipated as the norm for cases induced spontaneously in domestic animals with lower gauge needles and larger doses. Even extraneural injection of local anesthetics has been demonstrated to induce subperineurial edema.⁷ Fortunately, the subperineurial space is elastic and can accommodate a relatively large volume between the perineurium and the nerve fibers so that serious injury usually is avoided. Nevertheless, edema may spread within the fascicle and increase the permeability of perineurium to macromolecular tracers. Ultrastructural studies reveal mast cell degranulation and reactive fibroblasts in the nerve adjacent to the site of extraneural deposition. Eosinophils appear in the endoneurium, where edema is pronounced. Dystrophic axonal changes and demyelination can be seen. Axons are swollen by vesicles, organelles, and filaments and lipid droplets are abundant in both normal and disintegrating Schwann cells. These lipid inclusions are characteristic and suggest that the Schwann cells have sustained direct toxic injury.

Intravenous injection procedures may also lead to nerve damage. Injections deep to or around the external jugular vein may damage the neural contents of carotid sheath directly or by means of hematoma formation or infection. In the horse and cat, such complications have been manifest as Horner's syndrome, reflecting injury to the sympathetic component of the vagosympathetic trunk.

References are on page 494.

AMPUTATION NEUROMA

Amputation neuroma in humans is usually a result of traumatic interruption of peripheral nerves in which a large gap between the proximal and distal nerve stumps precludes effective axonal regeneration. In veterinary medicine, terminal neuromas most commonly result from surgical resections of the digital nerves that are performed in the horse to relieve the pain and lameness of navicular disease.¹ Abortive attempts at regeneration at the proximal nerve stump produce a firm bulbous terminal mass that is often several times the diameter of the nerve.

Ironically, these neurectomies that are performed to achieve analgesia can be marred by recurrence of pain and lameness due to formation of painful neuromas. The prevalence of this postoperative complication may reach 25% or higher.^{2,4} Although operative techniques have been successful in reducing the incidence of this complication,^{2,5-9} no surgical procedure actually confronts and eliminates the basis for neuroma formation.

Neuromas form because sensory fibers in the proximal

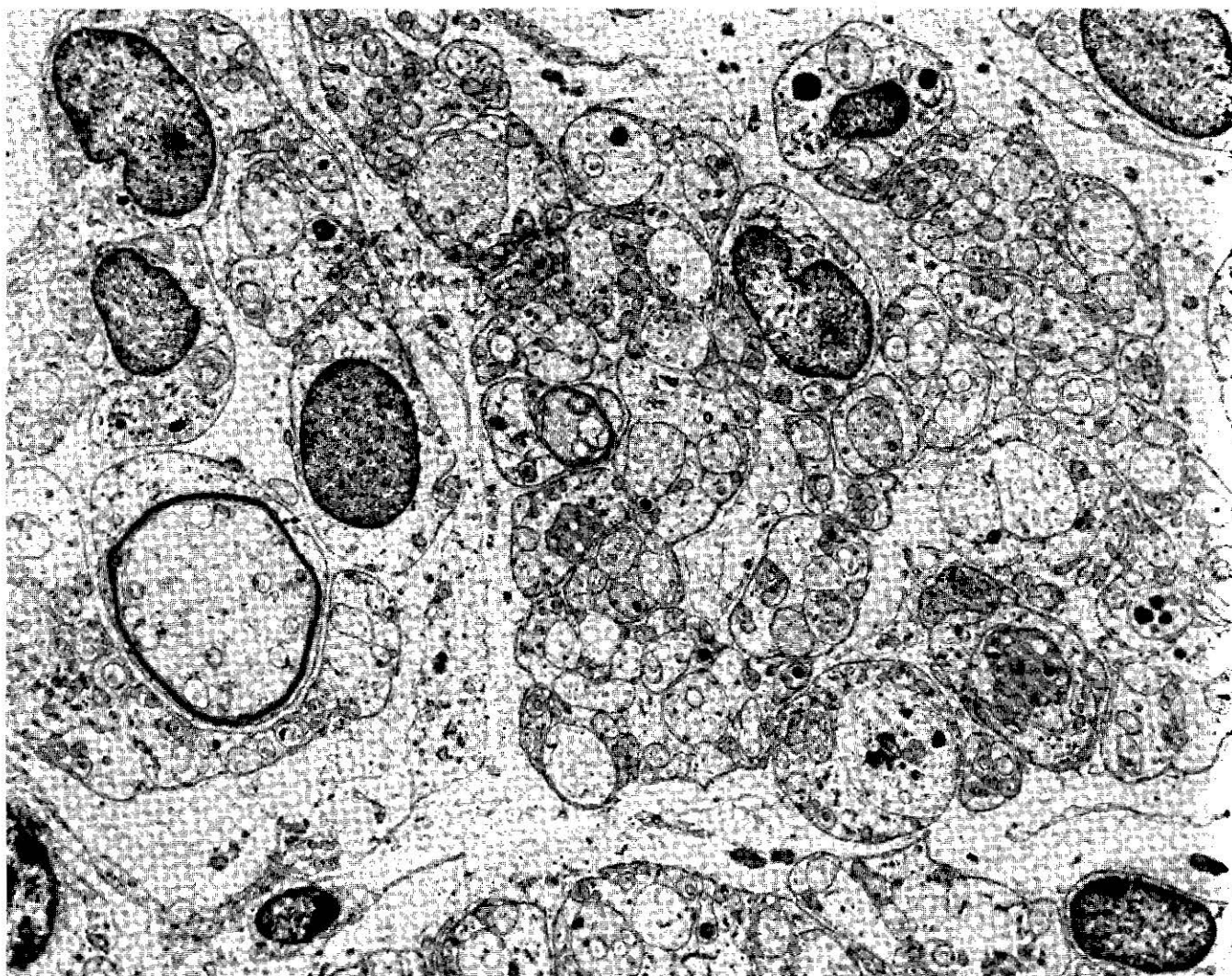


Fig. 7-31. Digital nerve amputation neuroma, horse. Note multiple axon sprouts; only a couple are myelinated. ($\times 5865$.)

nerve stump survive to produce a profusion of regenerating axon sprouts. It is the outgrowth of these nerve sprouts and associated supporting tissue that leads to neuroma formation.¹⁰ The pain emanating from neuromas has been associated with spontaneous impulse generation and marked hypersensitivity of the axon sprouts.¹¹⁻¹³ In laboratory rodents with experimentally produced neuromas, spontaneous impulse generation, heightened mechanoreceptivity, and adrenergic sensitivity combine to initiate afferent barrages that result in autotomy or self-mutilation.^{14,15} Hypersensitivity in transected nerves has been associated with discharges emanating from 10 to 20 μm axonal end bulbs that are called ectopic neural pacemaker nodules. These hypersensitive swellings (which can fire spontaneously) are thought to be derived from local accumulation of channel and receptor proteins that dam up at truncated axon ends after being delivered by anterograde transport from the sensory cell body.¹⁶

Microscopic study of terminal neuromas reveals many small fascicles that course variously within a dense and expansive collagenous matrix. With silver impregnation, axonal sprouts usually can be demonstrated within the fascicles. A neuroma that is painful cannot be distinguished morphologically from one that is not. Ultrastructural study of equine digital neuromas discloses that the fascicles are composed largely of proliferated Schwann cell cords, and many of these contain axon sprouts (Fig. 7-31). Most sprouts are unmyelinated, and some are degenerating. With time, the components of some of these innervated Büngner's bands separate slightly to form clusters of Schwann cells with single or multiple axon sprouts. The structural features of equine postneurectomy neuromas appear comparable to those in human amputation neuromas.^{17,18} As in other species, myofibroblasts have been observed in equine resection neuromas, and the possibility exists that these contractile cells may be involved in triggering neural discharges.¹⁹

Attempts have been made to abort the formation of equine postneurectomy neuroma formation by destroying the sensory neurons in the proximal stump. These attempts were dependent on retrograde delivery of lethal doses of neurotoxins, doxorubicin and ricin to the ganglionic cell bodies that sustain the sensory fibers in the proximal stump of the digital nerve.^{20,21} This retrograde axonal transport of neurotoxin to destroy selected neuron populations has been called suicide transport.²² Applications of doxorubicin in and on the proximal stumps of the digital nerves were largely ineffective in retrograde destruction of sensory cell bodies in the C8 and T1 spinal ganglia. In contrast, the toxic lectin ricin proved highly effective in retrograde destruction of these ganglionic neurons. The extreme toxicity of ricin, however, poses such a great systemic health hazard that its use in neuroma prevention cannot be recommended.²¹ Perhaps concurrent administration of antiricin antibody may eliminate the danger of systemic toxicity following intra-neural injection of this toxic lectin.²³ It may also be that modern surgical procedures such as laser neurectomy will prove effective enough at the proximal stump to eliminate further consideration of retrograde techniques.²⁴

References are on page 494.

CALVING PARALYSIS AND DOWNER COWS

This postparturient paralysis commonly occurs in heifers with dystocia associated with oversized fetuses.¹ Clinical signs include hind limb ataxia, weakness, and abduction or paralytic recumbency, the last being considered by some as a form of the "downer cow syndrome." Calving paralysis traditionally had been associated with bilateral compressive damage to the **obturator nerve** as it courses along the medial aspect of the shaft of the ilium. Such injury would result in paralysis of the adductor, pectineus, gracilis, and obturator muscles. Vaughan² found that bilateral section of the obturator nerve in a calf was not severely incapacitating, although the animal's hind limbs were abducted when it walked and especially when it ran. The same bilateral procedure in an adult cow, however, resulted in collapse, recumbency, total hind limb abduction, and inability to rise.² The latter experimental findings were seemingly supported by the common necropsy finding of hemorrhagic obturator nerves in postparturient "downer" cows. In subsequent experimental studies involving greater numbers of adult cattle, however, bilateral transection of the obturator nerves produced milder paresis.^{3,4} Postoperatively, these animals could stand and walk on non-slippery surfaces, yet they were compromised on slippery concrete, and while running their hocks were abducted as they advanced their hind limbs simultaneously. Clearly, the manifestations of impairment were to a great extent dependent upon whether the animal had good footing. On the basis of dissections, Cox and co-workers^{3,4} suggest that the **lumbar (L6) root of the sciatic nerve** was also prone to bilateral compressive injury as it courses on the ventral border of the wing of the sacrum.

Moreover, when obturator nerve transections were followed by surgical interruption of the lumbar root of the sciatic nerve, the resulting deficits, which included marked ataxia, fetlock flexion, and recumbency, were similar to those in many field cases of calving paralysis. The present consensus is that severe cases of calving paralysis (i.e., those that produce recumbency) result from simultaneous injury to the obturator nerve and the L6 root of the sciatic nerve.¹ These cows in recumbency are then predisposed to secondary compressive damage. Experimental production of recumbency for periods up to 12 hours in cattle with one hind limb drawn under the body results in ischemic necrosis of the hamstring muscles (especially the semitendinosus) and discoloration and fibrosis of the sciatic nerve caudal to the proximal femur. Peroneal nerve damage is evident clinically as fetlock flexion, but gross inspection of this nerve only rarely yields evidence of damage.⁵

It is now believed that the "downer cow syndrome" may be initiated by various primary disorders (e.g., calving paralysis, milk fever, fractures) that produce recumbency.⁶ With recumbency, secondary compressive damage to caudal thigh muscles and to sciatic and peroneal nerves further incapacitates the animal. The animal's condition may deteriorate even further as it struggles to rise and in so doing induces tertiary muscle tearing.

References are on page 495.

FEMORAL NERVE PARALYSIS IN CALVES AND HORSES

In **cattle**, the more prevalent nerve injuries involve the radial, sciatic, peroneal, femoral, and obturator nerves.¹ Although most of these injuries are common in juvenile or adult animals, unilateral femoral nerve paralysis has a high incidence in calves at birth. Charolais, Simmental, Maine Anjou, and Holstein calves born in dystocia to primiparous heifers are prone to develop contusions and partial or complete rupture of the femoral nerve and quadriceps muscles.^{2,3} The injury occurs when large calves in cranial presentation fail to enter the birth canal because their stifle joints become engaged at the brim of the pelvis. Traction used to deliver such calves causes hyperextension of the femur and stretching of the quadriceps muscle and its neural and vascular supplies. In a series of 21 calves reported by Tryphonas and colleagues,² the nerve damage was localized on the right. Gross necropsy findings include thickening of the femoral nerve, atrophy of the quadriceps and part of the psoas muscle, and patellar luxation. In calves alive at birth and surviving for some time thereafter, microscopic studies reveal Wallerian degeneration in fascicles of the femoral nerve, perineurial and endoneurial fibrosis, and neurogenic muscle atrophy.² Chromatolysis of the ventral horn cells develops in the L3-L5 spinal segments. In a recent unpublished case at Cornell, de Lahunta found that the causative injury was unilateral lumbar spinal root avulsion that provoked retrograde motor neuron death as well as chromatolysis. The

dorsal roots were interrupted central to the ganglia so that axonal degeneration occurred in the spinal dorsal funiculus but not in peripheral sensory nerve fibers of the saphenous nerve.

Bilateral femoral paralysis was reported after general anesthesia for orthopedic surgery in two horses. They presented with a characteristic stance.⁴ Their stifle, hock, and fetlock joints were semiflexed so that their hindquarters were dropped and they bore their weight on their toes. After 1 week, one animal recovered. The other animal's condition deteriorated and it was euthanized. Postmortem study revealed symmetrical epineurial hemorrhage along the femoral nerve where it crosses the deep face of the tendon of insertion of the psoas minor. Distal to the hemorrhage, the femoral nerve fascicles had well developed Renault bodies, but nerve fiber damage was not demonstrated. It was suggested that in both animals paresis was a manifestation of neuropraxia induced by compression. In one horse, recovery was thought to be prohibited by a complicating myopathy that developed with prolonged recumbency.

Similar bilateral femoral paralysis with perineural hemorrhages has been observed in mares with dystocias that produce sacroiliac luxations.⁵

References are on page 495.

ENTRAPMENT OF THE SUPRASCAPULAR NERVE IN HORSES

This subclinical neuropathy was found in the **suprascapular nerve** on one or both sides in 10 of 14 horses hospitalized for various orthopedic problems.¹ Dissections have revealed that as the suprascapular nerve is reflected around the neck of the scapula, it is bound by a band that is part of the strong fascial sheath that attaches the medial side of the supraspinatus muscle to the supraspinous fossa. At this point of reflection, neuropathic changes of varying severity were observed. Usually the changes were focal and

consisted of chronic demyelination and remyelination. In the more severely affected nerves, some clusters of regenerating axons were found along with profuse onion bulb formations. Changes were minimal in the nerve distal to the point of reflection. Swelling of the nerve at the point of reflection was associated with enlargement of the component fascicles caused largely by Renault body formation. The Renault bodies, which were most prominent in the nerves with the most severe lesions, seemed to arise as a result of nerve compression. This chronic neuropathy, which was characterized by focal and recurrent demyelination at a site of compression located between the edge of the scapula and a dense fascial band, has been identified as the first spontaneous entrapment neuropathy in domestic animals.

This subclinical entrapment neuropathy with no discernible shoulder muscle atrophy has been contrasted with classical **sweeney** (or swceney). This term is applied to the lateral instability of the shoulder and wasting of the supraspinatus and infraspinatus muscles that result from injury to the suprascapular nerve.² Trauma to the nerve on the cranial edge of the scapula occurs, for example, when a horse strikes an object or another horse with its shoulder.³ Additional identified sources of suprascapular nerve trauma have included pressure from poor-fitting collars in working horses, kicks, falls, and scapular fractures. Others believe that the axon degeneration is a result of overstretching the nerve when the shoulder or the leg is suddenly thrust backward.^{4,5} An accurate diagnosis can be made by EMG before muscle atrophy and shoulder instability become overt. Generally after suprascapular nerve injury, return to function through regenerative axonal growth requires approximately 70 days. Failure of functional restoration may be indicative of fibrous entrapment that prevents axon regeneration.⁶

References are on page 495.

Metabolic and nutritional disorders affecting the peripheral nervous system

GLOBOID CELL LEUKODYSTROPHY

Globoid cell leukodystrophy (GCL) or Krabbe's disease is an inborn error of metabolism in which a deficiency of lysosomal galactosylceramidase 1 (galactocerebrosidase β -galactosidase) is inherited as an autosomal recessive trait. This disease, which was first defined in humans, occurs also as a fatal disorder in **dogs**,^{1,2} **cats**,³ and **polled Dorset sheep**.⁴ Although GCL has been observed most often in Cairn Terriers and West Highland White Terriers,² other dog breeds are affected. These include Beagle,⁵ Bluetick Hound,⁶ Miniature Poodle,⁷ and Basset Hound.⁸

Whereas the CNS white matter changes (e.g., myelin loss, astrocytosis, and clusters of characteristic, PAS-positive globoid cells) are striking (see Chapter 5), in many canine cases there are substantial degenerative changes in peripheral and autonomic nervous components. The peripheral involvement is often manifest clinically. Signs that may develop as early as the second or as late as the seventh month can present in either of two major syndromes.² Some dogs develop severe pelvic limb paralysis early in the disease; in others cerebellar signs dominate in the early phase. Initial pelvic limb ataxia, which progresses to paraparesis,

results from both spinal cord and peripheral nerve involvement.² Considerable evidence of PNS involvement is suggested by some of the signs recorded in Bluetick pups afflicted with GCL.⁶ In two pups, signs included hind limb paralysis, loss or depression of the patellar reflexes, loss of withdrawal reflexes, and muscle atrophy.

Although histopathological examinations of peripheral, cranial, and sympathetic nerves from some dogs may fail to disclose lesions,⁹ changes at these levels are often marked. The PNS changes in the dog that were first described at the level of the spinal and trigeminal roots consisted of myelin loss, irregular swelling of axons, and clustering of the macrophage-like globoid cells in perivascular groups and in linear arrays between nerve fibers.¹ Changes in peripheral and sympathetic nerves may be evident grossly, severely affected trunks being clearly enlarged and whiter than normal.¹⁰ In such nerves, fibers are demyelinated segmentally, and axons may be swollen, fragmented, or lost. Globoid cells are found in the endoneurium and contain PAS-positive material and fragments of myelin sheath (Fig. 7-32, A).¹¹ Proliferation of endoneurial collagen is described in one report¹ but denied in another.¹¹ At the ultrastructural level, two characteristic forms of tubular inclusions can be found in the globoid macrophages and in the Schwann cells as well. The crystalline and curved inclusions that typify the disease ultrastructurally are believed to represent galactocerebroside. The involvement of the PNS in many animals makes sensory nerve biopsy a feasible diagnostic procedure. Changes in biopsy specimens, however, may be imperceptible with the light microscope and require the greater resolution of an electron microscope.^{12,13}

References are on page 495.

CANINE α -L-FUCOSIDOSIS

This lysosomal storage disease is unique in that it results in striking gross changes in both cranial and peripheral nerves. It was identified as a new storage disease in **Springer Spaniels** by Hartley and others in 1982.¹ A subsequent study by Kelly and colleagues² confirmed the initial clinical and pathological findings and demonstrated a severe deficiency of α -L-fucosidase activity in cultured fibroblasts and leukocytes.

Although progressive neurological signs may come on as late as 2 and 3 years of age,¹ the onset of behavioral abnormality may be perceived as early as 4 to 6 months.³ The early signs of excessive anxiety and unwillingness to accept restraint, together with temperament changes, depression, loss of learned responses, aimless wandering, and head tremors, reflect severe involvement of the CNS. Other manifestations, however, including hoarse bark or aphonia, depressed gag reflex, dysphagia, dyspnea, coughing, and pulmonary infections can be attributed to involvement of cranial nerves.

The gross findings at necropsy consist of striking enlargement of the cranial parts of the vagus, the cervical spinal nerves (especially those to the brachial plexus), and

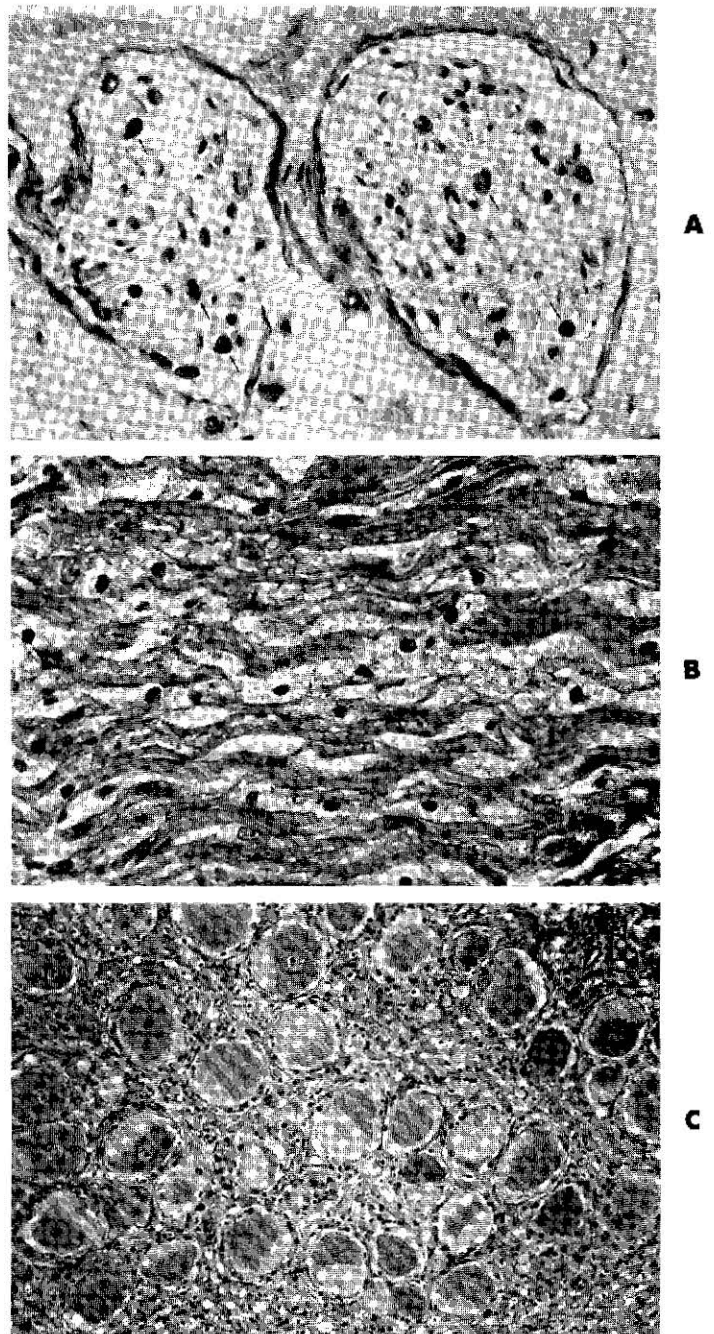


Fig. 7-32. A, Globoid cell leukodystrophy, dog. Globoid macrophages in endoneurium (arrows). (PAS, $\times 350$.) B, Fucosidosis, dog. Many vacuolated macrophages and fibrosis within dorsal root. (H&E, $\times 560$.) C, Fucosidosis, dog. Finely vacuolar storage substrate in neurons of spinal ganglion. (H&E, $\times 140$.)

the spinal ganglia.¹⁻³ The initial portions of the glossopharyngeal and hypoglossal nerves also may be thickened. In all affected nerves, the enlargement tapers off distally, although antemortem palpation of ulnar nerve enlargement may contribute to the diagnosis.³

Microscopic examination discloses that nerve enlargement is referable to abundant infiltration of the subepineurial

and endoneurial spaces with foamy macrophages and accumulations of a loose fibroedematous tissue among surviving nerve fibers (Fig. 7-32, B).^{1,2} In the spinal ganglia, prominent vacuolar distension of the sensory cell bodies (Fig. 7-32, C) contributes to the gross enlargement, along with accumulations of foamy macrophages and fibroedematous tissue. The vacuoles that swell the neurons and foamy macrophages appear empty for the most part but are the sites of accumulation of glycoasparagines and other fucose-containing substrates.⁴ Despite the pronounced interstitial changes in the cranial and peripheral nerves, surprisingly little axon degeneration or demyelination has been found.^{2,3}

Fucosidosis in Springer Spaniels is inherited as an autosomal recessive trait.⁵ Because carrier or heterozygous animals can be detected by plasma and leukocyte assays of α -L-fucosidase activity, successful screening programs can be conducted.⁶ This particular canine disorder holds great promise as a model for exploration of therapeutic regimens that may be applied to lysosomal storage disease in human beings.^{3,7}

References are on page 495.

CAPRINE AND FELINE MANNOSIDOSIS

Although the central nervous and visceral effects of this recessively inherited defect in glycoprotein catabolism are presented elsewhere, the peripheral neurological aspects of this **β -mannosidase deficiency** are reviewed here. This disease was first recognized in **Anglo-Nubian goats** in Australia by Hartley and Blakemore.¹ At birth, affected goats have multiple and severe neurological impairments that have included carpal flexion contractures, diminished muscle mass, and hyperextension of all four pasterns.^{2,3} This "arthrogryposis-like syndrome"¹ has been accompanied by electrical evidence of muscle denervation as well as microscopic demonstrations of minuscule skeletal muscle fibers, either scattered or clustered among fibers of normal size.^{2,3} These indications of motor neuronal involvement have been related to the presence of cytoplasmic vacuolation in the ventral horn cells as well as to degenerative changes in the intramuscular nerve fibers.³ Throughout the PNS, membrane-bound storage vacuoles occurred in Schwann cells. In sensory ganglia, neuronal cell bodies and satellite cells were also vacuolated.^{2,4,5} In these PNS components, the vacuoles with lucent or flocculent contents were coarse, but not unlike the cytosomes encountered in CNS cell types, for example, oligodendroglia.² In contrast to the CNS, however, there was no evidence of peripheral hypomyelination. Many myelinated axons, despite vacuolated Schwann cells, had a totally normal appearance. Some peripheral axons, however, contained aggregates of dense bodies. Spheroidal enlargements were especially prominent in distal and terminal axons. Studies concentrating on the sensory elements in the gingiva of affected kids revealed prominent accumulations of dense bodies in the Merkel cell end plates.⁶

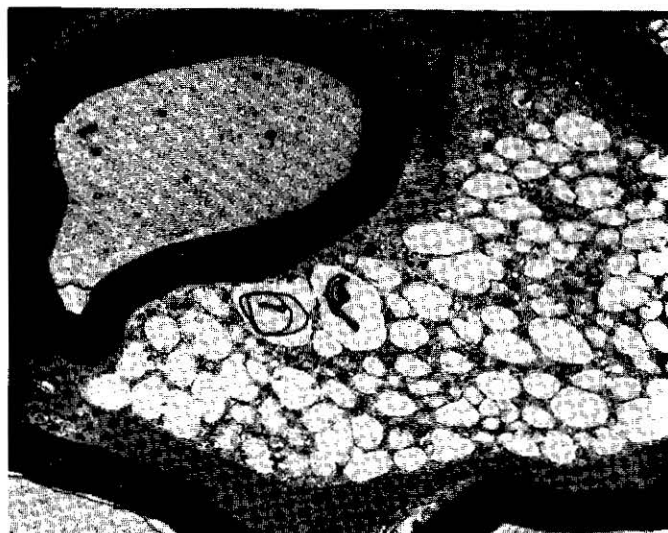


Fig. 7-33. Feline α -mannosidosis. Storage cytosomes in Schwann cell. ($\times 5850$.)

Free-ending axons and those in the cores of Pacinian corpuscles were also distended, as were preterminal portions of myelinated and unmyelinated axons in the gingival lamina propria. The origin of the dense bodies within the distended axons was not determined, although it was suspected that they might be derived from degenerated mitochondria.⁷ The presence of distal axonal spheroids with accumulations of dense bodies was thought to represent a breakdown in some phase of axonal transport—perhaps in the turnaround mechanism as described by Brimijoin.⁸

We have examined the PNS of two cats with **α -mannosidosis**.⁹ In addition to widespread CNS changes, vacuolated neurons were also observed in the spinal and enteric ganglia. Peripheral axonal degeneration was infrequent. Endoneurial macrophages and Schwann cells (Fig. 7-33) contained abundant vacuoles. Despite these abnormalities, megaesophagus in one cat was the only clinical sign referable to peripheral involvement.

References are on page 495.

FELINE NIEMANN-PICK DISEASE POLYNEUROPATHY

A demyelinating polyneuropathy has been described in young cats, between 4 to 7 months of age, afflicted with Niemann-Pick disease.¹ One cat with marked sphingomyelinase deficiency, increased tissue concentrations of sphingomyelin and cholesterol, and elevated brain gangliosides GM₂ and GM₃ presented chemical changes consistent with **type A Niemann-Pick disease**. The two other cats were related and thought to be afflicted with a variant of typical type A Niemann-Pick disease. The atypical findings included relatively small increases in hepatic and renal sphingomyelin, modest elevation in brain sphingomyelin, and no

reduction of sphingomyelinase activity in cultured fibroblasts of heterozygous relatives.

Peripheral neuropathy was suspected in these cats because all three presented with tetraparesis, hypotonia, and hyporeflexia. These signs were not recorded in earlier cases of feline Niemann-Pick disease in which cerebral and/or cerebellar dysfunctions predominated. Cerebellar signs, however, were also observed in two of the three cats. Electrodiagnostic testing revealed motor and sensory nerve conduction slowing. Electrical evidence of muscle denervation (i.e., fibrillations and positive sharp waves) was mild and not recorded in all muscles. Nerve biopsy revealed diffuse myelin degeneration with large ovoid cells aligned along denuded axons.

Gross findings at necropsy were limited to mild splenomegaly and moderate hepatomegaly. Histologically, aggregates of macrophage-like cells with refractile metachromatic granules were found in the splenic white pulp, lymph nodes, lamina propria of the intestines, lung, bone marrow, and thyroid and adrenal glands. Similar distension and metachromasia appeared in the renal corpuscles, distal convoluted tubule and bile duct epithelia, hepatocytes, Kupffer cells, small intestinal smooth muscle cells, and retinal ganglion cells. In the CNS, vacuolar and granular distension occurred in neurons, glia, endothelium, choroid plexus epithelium, and ependyma.

In the PNS, granular and vacuolar inclusions again were obvious in the neurons of the spinal and autonomic ganglia. In the spinal roots and cranial and peripheral nerves, there was extensive segmental demyelination of axons as well as remyelination. There was, however, little evidence of axonal degeneration. In the endoneurium, there was an abundance of macrophage-like cells laden with myelin debris as well as metachromatic granules. Electron microscopic examination revealed axons with thin myelin sheaths that were described as being surrounded either by actively phagocytic Schwann cells or macrophages that contained zebra bodies. The polyneuropathy in association with feline Niemann-Pick disease (type A and type A variant) were cited as the first described inherited primary polyneuropathy in the cat.¹

Niemann-Pick disease type C has also been identified in kittens.² In type C, as opposed to type A, sphingomyelinase deficiency is not the primary metabolic error. At present, the enzymological basis for Niemann-Pick disease type C has not been defined. In affected kittens, cerebellar signs predominated, and peripheral neurological deficits were not detected. Histopathology studies, in addition to neuronal and glial storage, disclosed widespread axonal spheroid formation in the CNS. Despite marked storage and swelling of spinal ganglion neurons (Fig. 7-34) and ventral horn cells, changes in the roots and nerves were sparse. At the level of the spinal roots, there was only scattered evidence of segmental demyelination in the form of denuded axon lengths associated with small linear arrays of macrophages. Many of the Schwann cells associated with intact myelin

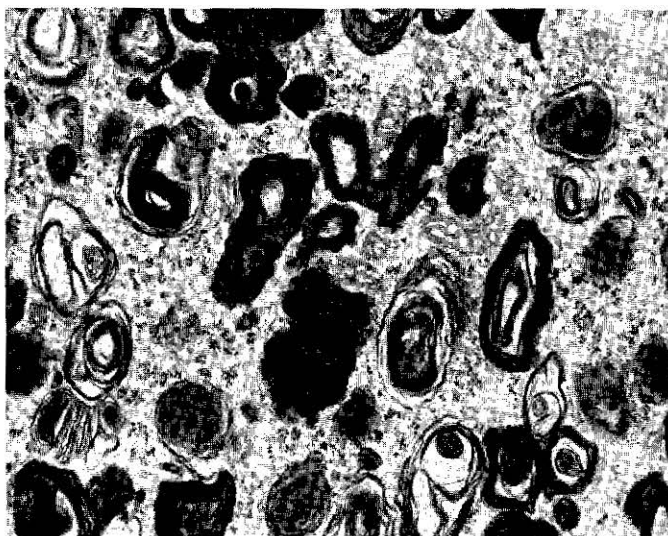


Fig. 7-34. Feline Niemann-Pick disease type C. Membranous cytosomes in a spinal ganglion neuron. ($\times 26,000$.)

sheaths contained partially extracted storage vacuoles. In the sciatic nerves, digestion chambers (which appeared infrequently) indicated that some axonal degeneration had occurred. Axonal spheroids, which were very abundant in the CNS, were rare peripherally.

References are on page 496.

ATYPICAL CANINE GM₂ GANGLIOSIDOSIS WITH MUSCLE WEAKNESS AND WASTING

Typically, canine GM₂ gangliosidosis has occurred as a recessively inherited disease in purebred dogs (e.g., German Shorthaired Pointer, Japanese Spaniel) and has manifested in the first or second year of life with progressive and diffuse CNS signs.^{1,3} Recently Rotmistrovsky and associates⁴ reported GM₂ gangliosidosis in a 20-month-old, mixed-breed bitch that developed signs of both CNS and PNS involvement. A littermate had died earlier with more severe but similar impairments. At 24 months, marked trembling was accompanied by muscle atrophy and fasciculations. The dog had difficulty rising and walking. The gait was spastic. The forelimbs were short-strided and excessively pronated. Postural reactions were deficient in all limbs, and the patellar reflexes were lost. Fibrillations and positive sharp waves were widespread on EMG, and motor nerve conduction velocities measured on the ulnar nerves were delayed at 38.7 m/second.

In keeping with the observed muscle fasciculations, weakness and atrophy, and reflex loss, there was substantial degeneration of myelinated axons in the peripheral nerves and in dorsal and ventral roots (Fig. 7-35). This axonal degeneration appeared in association with notable enlargement of both the primary sensory and lower motor neurons through accumulation of membranous cytoplasmic bodies. The cellular perturbations that eventuated in this unusual



Fig. 7-35. Atypical GM₂ gangliosidosis. Compacted Büngner's bands formed in the wake of axonal degeneration. ($\times 13,000$.)

amount of axonal degeneration remain to be defined. Moreover, the basis for the conduction delay was not obvious, as the possibility of primary or secondary segmental demyelination was not explored with osmicated teased-nerve preparations.

Although this case of GM₂ gangliosidosis was exceptional by virtue of its appearance in a mongrel and the notable signs of peripheral nerve degeneration, some regional muscle atrophy was detected previously in a case of GM₂ gangliosidosis in a Shorthair Pointer.³

The findings, save for the peripheral sensory involvement, in this adult mongrel bear some resemblance to atypical adult human cases of GM₂ gangliosidosis wherein there are signs of both upper and lower motor dysfunction.⁵⁻⁷ In humans, the phenotype of adult GM₂ gangliosidosis has been notably variable.⁷ This phenotypic variation may also be demonstrated in the future as numbers of adult canine cases are accumulated.

References are on page 496.

DIABETIC NEUROPATHY

Although neuropathies with diverse clinical presentations frequently accompany human diabetes mellitus,¹ in domestic animals **diabetic neuropathy** has been recognized only infrequently. In **dogs**, the neuropathy may be subclinical, or the manifestations can range from insidious to acutely progressive paraparesis with proprioceptive defects, depressed spinal reflexes, and muscle atrophy.² Collyer and Gripper³ described a severe case in which a postparturient bitch progressed from hind limb weakness to recumbency with loss of patellar and triceps reflexes. In **cats**, a more consistent clinical picture has included hind limb weakness with a characteristic plantigrade stance, depressed patellar reflexes, muscle wasting, and proprioceptive loss.⁴ Electro-

diagnostic studies in both dogs^{5,6} and cats⁴ revealed denervation potentials and nerve conduction velocity delays. Despite a guarded prognosis, resolution of the diabetes and neurological signs has been reported following insulin therapy.^{4,7}

Studies of the peripheral nerve changes have indicated a distal axonopathy.^{8,9} In dogs, study of longstanding cases with teased plantar nerve preparations revealed many short, intercalated internodes, which suggest remyelination after paranodal demyelination, as well as series of short, thinly myelinated internodes, which indicate regeneration after axon degeneration. Active degeneration of myelinated axons has been more prevalent in a juvenile case of diabetes with an acutely evolving neuropathy.⁶ Demyelinating changes were often observed, but it remains problematical to what extent these were primary, that is, independent of the axonal changes. Extensive review of the peripheral nerve changes in human diabetic neuropathy has disclosed nerve fiber degeneration that begins proximally in peripheral nerves and progressively increases to summate distally.¹⁰ Both axonal degeneration and segmental demyelination occur, but axon degeneration predominates. Demyelination is secondary to axon changes.

Studies on the causation of neuropathic changes in human diabetes mellitus have been complicated by the diverse peripheral neurological manifestations of this disease.¹ This diversity has suggested the existence of multiple pathogenic factors that might include vascular and mechanical factors as well as biochemical disturbances.¹¹ Biochemical aberrations currently receiving serious consideration in the pathogenesis include myoinositol deficiency, which is associated with a reduction in Na⁺-K⁺-ATPase activity in nerves and disturbances in protein metabolism in the perikarya, which might lead to distal axon degeneration. Such metabolic changes also have been proffered in the dog and cat as likely causes of axon and Schwann cell derangements.^{2,8}

References are on page 496.

HYPOTHYROID NEUROPATHY

Various cranial and peripheral nerve dysfunctions have been recorded in adult or aged dogs in association with **hypothyroidism**. The endocrine deficiency and the observed neural dysfunctions have not always been clearly established to occur in a cause-effect relationship. A frequent clinical association has been noted between laryngeal paralysis and hypothyroidism.¹⁻³ Remission of the paralysis in response to the thyroid therapy in many cases has supported a causal role of the hypothyroidism. Pathological studies on the recurrent nerves from affected dogs, however, have not been reported. In some dogs with hypothyroidism, laryngeal paralysis has been accompanied by evidence of peripheral neuropathy, such as hind limb ataxia, paresis, muscle wasting, and denervation potentials.^{1,4,5} In other dogs with hypothyroidism, there have been multiple cranial

nerve deficits (i.e., CN V, VII, VIII) that abated or resolved with L-thyroxine therapy.⁶ In two hypothyroid dogs with no observed cranial nerve deficits, hind limb weakness progressed to quadripareisis. Denervation potentials were obtained on EMG, and delayed motor nerve conduction velocities were also recorded.⁷ Both quadriparetic animals improved markedly on desiccated thyroid treatment.

The nature and range of the pathological changes in hypothyroid dogs with motor deficits have not been studied thoroughly in this treatable illness. The difficulty in discerning neuropathic from myopathic changes is illustrated in a muscle biopsy study in two quadriparetic dogs. The biopsy samples yielded changes consistent with denervation in one dog (i.e., atrophy of type I and II muscle fibers) and changes indicative of myopathy (i.e., type II myofiber atrophy) in the other.⁷ A sural nerve biopsy in the dog with muscle denervation changes contained evidence of myelin degeneration. However, it was not determined whether this degeneration occurred segmentally or as part of Wallerian degeneration. Necropsy studies in two hypothyroid dogs with signs of diffuse lower motor neuron disease provided evidence of distal axonopathy.⁴ Because both dogs also were afflicted with malignancies, it was unclear if the distal axonal changes were manifestations of a paraneoplastic effect, hypothyroidism, both, or, perhaps, neither. Teased preparations of peripheral nerve biopsy specimens from two dogs with hypothyroidism and laryngeal paralysis revealed evidence of demyelination and remyelination. In these animals, it was not clear if the myelin changes were primary or secondary to axonal changes.⁵

In humans with hypothyroid polyneuropathy, pathological studies have resulted in some apparent divergence in the findings. Dyck and Lambert,⁸ in light- and electron-microscopic studies of sural nerve biopsy specimens from two patients with hypothyroid polyneuropathy, found evidence of segmental demyelination and remyelination. Occasionally, degenerating axons also were seen. Characteristic aggregates of glycogen were found ultrastructurally in the Schwann cells along with clusters of mitochondria, lipid droplets, and lamellar bodies. Glycogen granules and abnormal mitochondria were also found in axons. The demyelinating changes might be primary, resulting from a metabolic derangement of the Schwann cells, or could be secondary to a disorder in the nerve cell body or axon.⁹ Increased numbers of mucoid Renaut bodies also were found in some biopsied nerves.^{10,11} Biopsy studies on a patient with hypothyroid polyneuropathy lead Shirabe and others¹² to conclude that the observed segmental myelin loss was more likely due to a metabolic disorder of Schwann cells than to compression through increased deposition of mucinous substances within the nerves.

In a study of four human patients with polyneuropathy and hypothyroidism, electrodiagnostic findings of denervation potentials and moderate slowing of nerve conduction velocities were correlated with biopsy findings of axon

degeneration.¹¹ These investigators found no evidence for primary demyelinating disease and suggested that the observed neuronal changes were consistent with a dying-back neuropathy, possibly due to a defect in slow axonal transport. A recent study of rats with induced hypothyroidism correlated reduced motor action potentials with mild and reversible dissolution of neurotubules in myelinated axons.¹³

References are on page 496.

PANTOTHENIC ACID DEFICIENCY IN SWINE

Pantothenic acid deficiency may occur under natural conditions in pigs on rations based on corn.¹ With experimental induction of pantothenic acid deficiency, digestive signs (e.g., anorexia and diarrhea) may precede clinical manifestation of neurological impairment.² Such impairment appears initially as hind limb ataxia and incoordination. The most characteristic clinical feature of pantothenic acid deficiency in pigs is the development of a goose-stepping gait. The hind legs are placed more widely apart than usual, and, when the hips are flexed, the knees are held stiffly in extension and lifted 6 to 9 inches off the ground.³ Eventually the animals may be unable to walk or stand.⁴

Postmortem study reveals that degenerative changes in the nervous system are largely confined to the primary sensory neurons. Spinal motor neurons are spared. Examination of peripheral nerves discloses degeneration of myelinated fibers and macrophage removal and degradation of myelin debris. Study of the spinal ganglia reveals chromatolysis, shrinkage, and disappearance of sensory cell bodies. Sites of sensory cell body loss are marked by focal aggregates of satellite cells and macrophages.³ Cell body loss never exceeded 20% of the total population of a ganglion. The chronology of neural lesion development is debated. According to Follis and Wintrobe,⁴ the earliest change appears as chromatolysis of the large and small cell bodies of the spinal ganglia; degeneration of axons in the peripheral nerves then follows, and the dorsal column degeneration occurs still later. The sensory cell bodies are identified as the foci of initial damage. Swank and Adams,³ however, describe the progression differently. They observe that nerve fibers in the distal portions of the peripheral nerves degenerate prior to the development of significant changes in the dorsal roots, spinal ganglion, or dorsal funiculus. Degeneration commences, they found, in the distal portions of the largest myelinated axons. Swank and Adams³ noted that the degeneration of the primary sensory neurons could easily explain the observed ataxia, but attributed the spastic "goose step" to lesions at a higher level that escaped histological detection.

References are on page 496.

RIBOFLAVIN DEFICIENCY IN CHICKENS

The association between **riboflavin deficiency** and "curled toe" paralysis in young poultry has been long rec-

ognized.¹ More recently, studies of rapidly growing chicks on riboflavin-deficient diets have examined the nature of the underlying peripheral neuropathy.^{2,3}

Chicks in advanced stages of paralysis are unable to extend their hocks, stand, or walk in plantigrade fashion, and the toes on one or both feet are curled under and flexed. Diarrhea and stunting are also noted in affected chicks. Mortality may be high after 3 weeks, although usually improvement has been observed in birds with experimental deficiency.²

At necropsy, the peripheral nerves appeared grossly enlarged. Microscopic studies of peripheral nerve sections and teased preparations revealed a demyelinating neuropathy that is accompanied by endoneurial edema and only scattered axon degeneration. Schwann cells appeared enlarged initially, and large segments of the myelin sheath formed multiple protrusions into the Schwann cell cytoplasm as a prelude to fragmentation of the sheath and segmental demyelination. Affected Schwann cells were hypertrophied and contained myelin debris and many lipid droplets. The extent to which macrophages are involved in myelin degradation has not been defined fully. Remyelination in nerves of affected chicks was signaled by progressive development of thin myelin sheaths. This remyelination was correlated temporally with clinical improvement. Remyelination was thought to reflect a declining riboflavin requirement with increasing age and decreasing growth and an age-associated increase in intestinal synthesis of this vitamin.

It has been suggested that the basis for Schwann cell dysfunction and demyelination is a deficiency of riboflavin-derived coenzymes. Diminished levels of flavin-adenine dinucleotide (FAD) and flavin mononucleotide (FMN) would lead to impaired oxidative phosphorylation. This diminished level of cellular energy could impair Schwann cells at a time of rapid growth and heightened metabolic demand.

References are on page 496.

INHERITED NEUROAXONAL DYSTROPHY IN C₆-DEFICIENT RABBITS

A subacute motor neuropathy was observed in some of the offspring of rabbits that were genetically deficient for the C₆ component of complement.¹ Affected rabbits at 2 to 4 months of age developed progressive hind limb weakness that in some eventuated in quadriplegia and death. Postmortem studies revealed severe and rather selective degeneration of motor axons in the sciatic nerve and its tibial nerve branch. Degeneration of these myelinated axons appeared to increase distally. Many of the intact myelinated axons in the sciatic nerve contained subaxolemmal tubulovesicular structures, but these axons were not swollen by these abnormal inclusions. No changes were detected in the spinal motor neurons or the neurons of the spinal ganglia.

Pathological changes were not limited to the peripheral nerve. Swollen dystrophic axons were widespread in the

gray matter of the CNS, for example, in dorsal column nuclei, bulbar nuclei, cerebellum, basal ganglia, thalamic nuclei, and frontal cortex. Axon spheroids with abnormally thin myelin sheaths were often situated paranodally. Some axonal swellings appeared to be situated presynaptically. Ultrastructural examination disclosed that the dystrophic axons were filled with tubulovesicular material, parallel membranes, normal and abnormal mitochondria, amorphous material, and dense bodies. Fragmenting central axons were seen only rarely. The authors suggested that the severe muscle weakness and wasting resulting from degeneration of peripheral axons may mask signs of dysfunction associated with central axonal dystrophy. The central and peripheral distribution of the pathological changes in this inherited disorder of rabbits contrasted with that recorded in human neuroaxonal dystrophy but resembled that reported in distal axonopathy of Birman cats.²

References are on page 496.

NEUROPATHY ASSOCIATED WITH INHERITED HYPERCHYLOMICRONEMIA IN CATS

An unusual form of compressive neuropathy has been reported in cats in association with **inherited hyperlipoproteinemia**.¹ The hyperchylomicronemia in affected cats has been associated with a lipoprotein lipase deficiency that appears to be inherited as an autosomal recessive trait. The most consistent clinical feature—other than marked fasting hyperlipemia, which gives the blood a cream of tomato soup appearance—is the presence of various paralyses. Peripheral, cranial, and sympathetic nerves have been affected, usually causing unilateral deficits. Impairments have included Horner's syndrome; facial, trigeminal, and recurrent laryngeal paralyses; and proprioceptive and motor losses associated with the tibial, peroneal, femoral, and radial nerves.

Postmortem studies revealed that lipid accumulation, leading to xanthomata, may be found in many organs, including liver, kidney, and spleen.² Affected nerves and roots were grossly thickened and distorted by encroaching focal masses of red-brown xanthomatous tissue. These compressing nodular masses appeared to represent organizing hematoma. The lipid in the extravasated blood evoked granulomatous reactions that were characterized by large, vacuolated macrophages in association with a coagulum that also contained lipofuscin, hemosiderin, and crystals of triglycerides and cholesterol. The granulomatous masses, which usually remained outside the perineurium, appeared to compress the adjoining nerve fascicles, resulting in degeneration and loss of myelinated fibers. The severity of fiber loss varied widely among fascicles. A low-fat diet for 2 to 3 months was effective in resolving the paralyses and reducing the blood lipid levels in three cats with hyperchylomicronemia.

References are on page 496.

NEUROPATHY ASSOCIATED WITH PRIMARY HYPEROXALURIA IN CATS

This recessively inherited disease of shorthaired **domestic cats** is characterized by L-glyceric aciduria and intermittent hyperoxaluria. It appears to be a feline analogue of **primary hyperoxaluria type 2** in humans as this feline disorder has the same enzymatic defect, a deficiency of D-glycerate dehydrogenase.¹

Clinical signs appeared abruptly between 5 and 9 months. In affected kittens, anorexia, dehydration, and weakness developed over a few days. Abdominal palpation, which revealed irregular and enlarged kidneys, also evoked evidence of pain. These acutely ill kittens were depressed and in poor condition. On neurological examination, profound weakness was the most consistent finding. Deficient postural reactions such as hopping and reduced reflexes such as withdrawal responses were observed but with less regularity. The panniculus response, however, was absent in seven of eight affected kittens.

On postmortem study, the kidneys were typically enlarged with irregular outlines. White oxalate crystals were visible grossly in the renal pelvis of one cat, but microscopic study in all revealed many birefringent crystals in the urinary tubules. Weakness in these cats was associated with large swellings along the proximal length of the axons of the spinal motor neurons. These swellings, which were caused by marked accumulations of neurofilaments, were found also in axons in the ventral roots and intramuscular nerves; they were very abundant in the spinal ganglia. There was also evidence of Wallerian degeneration in the peripheral nerves and denervation atrophy of muscle.

The proximal axonal alterations in these kittens were compared to those previously described in Brittany Spaniels with spinal muscular atrophy and in intoxications with compounds such as 3,3'-iminodipropionitrile.

References are on page 497.

Poisoning and the peripheral nervous system

LEAD POISONING

The manifestations and the course of lead poisoning vary among the domestic species. The problem is most common in cattle, where it occurs with indiscriminate ingestion of a large quantity of lead (e.g., in paint, batteries, machinery oil) and is manifest as an acute encephalopathy.¹

Chronic lead poisoning with cranial and peripheral nerve paresis has been reported often in **horses**.²⁻⁵ Intoxication usually has been associated with protracted contamination of forage brought about by airborne emissions from smelters.⁴ Months or years may elapse before signs appear in horses grazing on contaminated areas. Clinical deficits observed include paralysis of the lip and anal sphincter. Laryngeal hemiplegia or paralysis is reported and may cause collapse on exercise. Pharyngeal paresis may be manifest as nasal regurgitation and result in aspiration pneumonia. Terminally, horses may be incoordinated, tremulous, and unable to swallow.⁴ Experimental attempts to reproduce the cranial nerve palsies ascribed to chronic lead poisoning in horses have not duplicated the field observations.⁶ Moreover, descriptions of the microscopic changes in the affected cranial and peripheral nerves from paretic horses are not available in the literature.

In **dogs**, lead poisoning usually is a disorder of young animals associated with allotriophagic ingestion of paint, linoleum, and the like. As in cattle, signs of lead toxicity (e.g., behavioral change and convulsions) develop acutely

and are consistent with extensive cerebral involvement characterized by vascular damage that may culminate in laminar necrosis.^{7,8} Although peripheral nerve lesions have been recorded in dogs with lead poisoning, the incidence is apparently low. Bratton and Kowalczyk⁹ report that megacosophagus occasionally has been associated with canine lead poisoning and suggest that this is a result of paralysis. Extant descriptions of the peripheral changes are brief and indicate axon degeneration.^{8,10} Chronic, low-level, oral administration of lead to dogs has failed to induce either toxic polyneuropathy or encephalopathy.¹¹

Spontaneous lead poisoning is rare in the **cat**.¹²⁻¹⁴ Paint and pottery glaze have been identified as sources of lead. In Rhodesia, multiple cases in both dogs and cats occurred in a lead-mining area.¹⁵ As in the dog, digestive and nervous signs occur in the cat.^{16,17} The recorded neurological manifestations (e.g., anxiety, hysteria, seizures, blindness), however, reflect central nervous disturbances. In experimental intoxications of cats, Hong¹⁸ found extensive cerebral cortical neuronal necrosis and Purkinje cell necrosis, but no clear-cut electrical or pathological evidence of peripheral nerve involvement. Nevertheless, one case of feline megacosophagus has been attributed to lead neuropathy.¹⁹

Clearly, the clinical and pathological manifestations of lead poisoning vary with species, age, and the levels and rates of intake. Krigman and colleagues²⁰ have reviewed the variations among laboratory species in peripheral nerve

changes in lead poisoning. Although segmental demyelination of peripheral axons is prominent in the guinea pig and rat, this change is minimal in the cat and replaced by Wallerian degeneration in the rabbit. Most recent experimental studies have concluded that Schwann cell damage is the primary insult in the pathogenesis of lead polyneuropathy.²¹⁻²⁴ The early ultrastructural Schwann cell changes are reactive; the cytoplasmic volume and organelles increase. Schwann cell intranuclear inclusions form next. By binding free lead, the lead-protein complex in these inclusions may have a protective effect. Degenerative Schwann cell changes appear after the inclusions and include cytoplasmic swelling and organelle degeneration. The degenerative Schwann cell changes precede the breakdown of the myelin sheath by a considerable interval. Macrophages invade to strip the disintegrating myelin from the axon. After their focal destruction, the Schwann cells are replaced; Schwann cells originating from adjoining internodes proliferate, wrap around the demyelinated axon segments, and restore the myelin. The proliferation of Schwann cells is sustained with the persisting demyelination of chronic lead poisoning. This proliferation leads to onion bulb formation as supernumerary Schwann cells are margined to form concentric lamellae around the axon.²⁴ In the PNS, lead-induced vascular endothelial damage and endoneurial edema occur after demyelination has begun. Breakdown of the blood-nerve barrier occurs relatively late, and the ensuing endoneurial edema is considered an epiphenomenon in the pathogenesis of the segmental demyelination.^{22,24,25}

References are on page 497.

THALLIUM POISONING

Thallium, a heavy metal, in the form of salts thallous sulfate or acetate had been used as the active ingredient in fungicide, pesticide, and rodenticide preparations. Thallous sulfate often was added to corn to make an effective rodent bait, and in this form it presented a hazard for domestic animals and humans. Cats and dogs were exposed by eating thallium-poisoned vermin.

In 1965, the U.S. Department of Agriculture banned the general distribution of such rodenticides, and their manufacture was stopped in 1972. As a result, the incidence of thallium poisoning has been reduced greatly in the United States.¹ Nevertheless, occasional cases may still occur.²

The clinical manifestations of thallium intoxication reflect the involvement of most organ systems but are dependent upon the dose and duration of exposure. In acute cases, gastrointestinal signs may occur exclusively or predominantly. Cutaneous, respiratory, and neurological signs commonly present in cases with longer duration. In **dogs**, the range of clinical signs runs from anorexia, vomiting, and depression in the acute stages to striking skin changes, dyspnea, and neurological manifestations with cases of longer duration.³ A similar range of systems involvement is recorded in **cats**, as gastrointestinal signs appear acutely at 2

to 3 days after ingestion, whereas skin lesions typically characterize subacute and chronic cases.^{4,5} Neurological signs were often concurrent with characteristic erythematous and scaling skin lesions. These signs in dogs and cats include hyperesthesia, hyperexcitability, ataxia, incoordination, tremors, paresis or paralysis of the hind limbs, and seizures. Whereas many of the preceding deficits are attributable to CNS involvement, peripheral and cranial nerve changes occur also.

In spontaneous canine and feline cases of thallium poisoning, the CNS changes are described as chromatolysis, neuronophagia, and edema scattered throughout the cerebrum and cerebellum.^{3,5} The degenerative peripheral and cranial nerve changes in spontaneous cases have not been described in depth. Focal distension of the myelin sheaths is coincident with swelling and occasional fragmentation of axons.

In cats receiving subcutaneous injections of thallous acetate, Kennedy and Cavanagh⁶ noted ataxia and hypotonia as the chief clinical abnormalities. In these experimental intoxications, thorough pathological study revealed distal degeneration of the axons of the primary sensory neurons. The degeneration affected both the central and distal branches of the primary sensory neurons. Chromatolysis occurred secondarily in the spinal and trigeminal ganglia but in no more than 5% of the cell bodies. Involvement of the central branches of the sensory neurons was evident in the dorsal columns of the cervical spinal cord, where the longer axons of fasciculus gracilis were involved to a greater extent than the axons of the fasciculus cuneatus. A similar pattern of dorsal column degeneration in humans had earlier indicated a distal axonal degeneration.⁷ Unlike the cat, in humans motor neurons also were affected as chromatolytic changes appeared in the facial and hypoglossal nuclei and the ventral horns of the lumbosacral spinal cord.

The toxic effect of thallous salts resides in the ability of the thallium ions to compete with potassium ions. It may be that Tl^+ in binding for K^+ in Na^+/K^+ ATPase inhibits the enzyme's activity or that thallium's deleterious effects are due to the binding of sulfhydryl groups. Studying the ultrastructural effects of thallium on organotypic cultures of spinal cord-ganglia-nerve-muscle combinations, Spencer and others⁸ found that axonal mitochondria enlarge. Next, the matrix space becomes prominently swollen, transforming the mitochondria into large axonal vacuoles. These vacuoles coalesce to form massive, single, membrane-bound, intra-axonal compartments that result in enlargement of the axonal diameter. The relationship of these striking in vitro mitochondrial lesions to the in vivo toxicity, however, is not defined.⁸

References are on page 497.

MERCURY POISONING

In animals, most intoxications have occurred because of **alkylmercurial compounds**. In **farm animals** the exposure

has come through ingestion of seed grains that had been treated with alkylmercurial fungicides.¹ **Dogs and cats** have been poisoned by feeding on fish and shellfish from mercury-polluted waters. Cats, dogs, and birds developed signs of poisoning when hundreds of human cases occurred in the 1950s with the consumption of methylmercury-contaminated fish in the Minamata Bay area and Niigata District of Japan.² In some cases of environmental contamination with organic and inorganic forms of mercury, signs of poisoning have been manifest in cats before symptoms appeared in human beings.^{3,4}

Neurological signs in alkylmercury poisoning include incoordination, ataxia, intention tremors, weakness, blindness, and seizures. Many of the clinical findings may be associated with the neuronal necrosis that develops in the middle laminae of the cerebral cortex and the granular layer of the cerebellum.⁵

In some species, neuronal degeneration also develops in the spinal and trigeminal ganglia. Chronic methylmercury intoxication in a **horse**,⁶ in addition to cerebellar signs (e.g., hypermetria), produced hyperesthesia and proprioceptive deficits. In this aged gelding, cerebral cortical neuronal necrosis and loss of cells in the granule layer of the cerebellum were accompanied by extensive loss of large neurons in the spinal ganglia and marked proliferation of satellite cells. Additional evidence of loss of primary sensory neurons appeared as axon degeneration in the spinal cord, both in the dorsal root entry zone and dorsal funiculus. Substantial degeneration and loss of cell bodies in the spinal ganglia also has been described in experimental alkylmercury intoxications in **swine**.^{1,7} These changes in the sensory cell bodies were accompanied by axonal degeneration in peripheral and spinal nerves. Charbonneau and associates⁸ failed to find any peripheral nerve changes in cats with induced subacute methylmercury toxicity, yet Gruber and others³ demonstrated prominent Marchi staining in the fasciculus cuneatus in cats with chronic methylmercury poisoning. Although components of the PNS were not studied, the axonal degeneration in the fasciculus cuneatus would be consistent with degeneration of sensory neurons in spinal ganglia. Davies and associates⁹ studied the spinal ganglia and peripheral nerves in dogs with subacute methylmercurialism and found no significant changes.

Experimental studies of mercury intoxication indicate that the primary sensory neurons are a preferred target of methylmercury intoxication in laboratory species such as the rat and the rabbit. These studies have also disclosed that the PNS changes are those of a neuronopathy rather than an axonopathy.^{10,11} The axon degeneration that extends along the entire fiber length is a consequence of cell body degeneration. Herman and associates¹⁰ observed that changes appeared first in the cell bodies of the spinal ganglia. There is a loss of Nissl bodies as the neurons became pale and vacuolated with eccentrically located nuclei. Dying neurons are engulfed by satellite cells and macrophages.

Nageotte nodules form in the wake of neuronophagia. Ultrastructural studies of the spinal ganglia of affected rats and rabbits reveal a disorganization of the linear cisternal arrays of rER that normally form the Nissl granules.¹⁰⁻¹² The cisternae then lose their ribosomes, and the rER is lost from the neuron periphery, leaving a finely granular material in its stead. In some degenerating cells there is a total loss of rER as well as vacuole formation.^{11,12} The loss of ribosomes has been correlated with depressed amino acid incorporation into protein.^{13,14} Jacobs and colleagues¹² suggest that mercury may act at the level of the ribosome by binding to sulfhydryl groups that are exposed and reactive during peptide synthesis. Whereas the high lipid solubility of methylmercury can explain its entry and impact on the cerebrum and cerebellum, the rapid and selective effect of this toxin upon ganglionic cell bodies has been associated with the lack of a vascular barrier in the spinal ganglia.¹⁵ The possibility of retrograde axonal transport of protein-bound mercury from nerve endings is diminished by the autometallographic demonstration that mercury deposits are not limited to nerve cells in the spinal ganglia of intoxicated rats.¹⁶ Jacobs¹⁵ also found that degeneration of cell bodies and fibers occurs in autonomic and myenteric ganglia, neural elements that are also unprotected by vascular barriers. It is tempting to speculate that autonomic and enteric neuronal degenerations may develop in other species (e.g., the pig) and contribute to the digestive abnormalities recorded in methylmercury poisoning.

References are on page 497.

PYRIDOXINE POISONING

Pyridoxine (vitamin B₆) is an essential water-soluble vitamin and a coenzyme for many decarboxylation and transamination reactions.¹ Although of low intrinsic toxicity, the administration of megadoses of vitamin B₆ can induce neurological disease. In intoxicated dogs, ataxia is a prominent sign.² It develops earlier and more severely in the pelvic limbs.³ Some dogs display marked proprioceptive loss as they walk on the dorsum of their paws. The gait is usually dysmetric and the stance base-wide.³ Tendon reflexes may be lost, and severely ataxic animals fall frequently.² Eventually, some dogs may be unable to walk, but these animals are not weak.⁴

At necropsy, the dorsal funiculus on gross inspection may present a white opaque appearance.⁵ This finding reflects the axonal degeneration and astrocytosis that typify irreversible, longstanding changes in the dorsal columns. The Wallerian-type degeneration observed microscopically in the dorsal funiculus can be found also in the spinal tract of the trigeminal nerve, the dorsal roots, and fascicles of the peripheral nerves.⁵ Studies in rats disclose that, just 2 to 3 days after exposure to large doses of pyridoxine, degeneration appears in the longest and largest sensory nerve fibers in the dorsal funiculus and peripheral nerves.⁶ This degeneration appears first in distal portions of axons in the fas-

ciculus gracilis.⁶ In overdosed dogs, clinical signs and underlying pathological changes may not appear until 9 or 10 days.^{4,7} The extent and nature of the degenerative changes in the cell bodies of the sensory ganglia of intoxicated dogs have been reported variously. Hoover and Carlton^{5,8} found that the major degenerative changes were in peripheral and central projections of the sensory neurons, whereas the changes in the cell bodies per se were minimal and characterized by central chromatolysis and a few Nageotte nodules. Earlier, Antopol and Tarlov² had depicted widespread chromatolysis in the spinal ganglia but thought that these changes were preceded by fiber degeneration in the dorsal columns. Krinke and others¹ found widespread vacuolar degeneration in the cell bodies in the spinal and trigeminal ganglia and indicated that the observed degeneration of the larger caliber axons occurred later and secondarily. Ultrastructural study of the ganglionic neurons by Montpetit and associates⁷ revealed perikaryal masses of neurofilaments as well as granular aggregates composed of mitochondria, vesicles, dense bodies, and other matter. These cell body changes appeared to be preceded by neurofilamentous distension of the proximal axon.

The precise means by which pyridoxine is toxic to sensory neurons is unknown. Based on the sequence of change, it has been suggested that the target site for the toxic effect is located in the axon hillock or initial segment.⁶ Selective injury to primary sensory neurons with sparing of CNS neurons has been attributed to the absence of a vascular barrier in the ganglia, which would permit pyridoxine accumulation.¹ It also has been noted that differences in pyridoxine intermediary metabolism in ganglionic neurons could explain their vulnerability.⁷

References are on page 498.

VINCRIStINE NEUROPATHY

Vincristine sulfate, an alkaloid obtained from the periwinkle plant, *Vinca rosea*, has proved efficacious in the treatment of leukemia, lymphoma, and various solid tumors. In human beings, it is said that vincristine induces peripheral neuropathy in almost every patient who receives the drug.^{1,2} Recovery from the impairments of vincristine neuropathy is usual and begins when the drug is withdrawn. Although the dog has been observed to be more resistant to the neurotoxic effects of vincristine, under certain circumstances peripheral neuropathy may develop.³ The case in point, a 12-year-old Golden Retriever with cutaneous lymphoma, was treated with standard doses of vincristine for 16 weeks. Although many dogs sustain more protracted courses of vincristine without toxicosis, this animal developed neurological deficits. These included hind limb weakness, ataxia, and depressed reflexes. Electrodiagnostic studies revealed widespread denervation potentials, reduced sciatic motor nerve conduction velocity, and evoked muscle potentials that were polyphasic and reduced in amplitude. An initial peroneal nerve biopsy revealed marked loss of my-

elinated fibers and endoneurial fibrosis. After vincristine therapy ceased, clinical neurological signs regressed 10 weeks later, although electrodiagnostics and a contralateral peroneal nerve biopsy at that time revealed persisting abnormalities. In the second biopsy specimen, however, paranodal demyelination and remyelination were seen.

Although pathological assessment in this canine example of vincristine neuropathy was limited to light microscopic study of biopsy material, the characteristic lesions of this drug have been thoroughly defined in humans and laboratory species.⁴⁻⁷ The neurofibrillary degeneration that typifies vincristine and other mitotic spindle inhibitors (e.g., vinblastine, colchicine, and podophyllotoxin) is marked ultrastructurally by loss of neurotubules and accumulations of neurofilaments. The degree of clinical impairment and the sites and intensity of pathological change vary with dose, route of administration, duration of therapy, and species.⁸ For example, in human patients undergoing vincristine treatment, the initial signs of neurotoxicity include loss of the Achilles tendon reflex and distal paresthesias.² If the drug is continued, muscle pain, weakness, and sensory impairments ensue; subsequent administration leads to generalized weakness and even to quadriparesis. Intrathecal administration has been associated with aggregation of neurofilaments in neuronal cell bodies of the brain stem and ventral horn of the spinal cord.^{4,5} Large crystalline masses, ultrastructurally observed to be in continuity with neurofilament bundles, appear with the light microscope as acidophilic rhombohedral inclusions in the cytoplasm of affected cell bodies.⁹ In chronic intravenous vincristine intoxication in the cat, the major pathological change consisted of focal giant axon formations due to malaligned accumulations of neurofilaments.⁷ These swellings were found mostly along the proximal course of the peripheral nerve fibers, whereas examples of Wallerian degeneration occurred distally. Perikaryal changes were not observed. As in the reported canine case, light microscopic and teased-nerve fibers in intoxicated humans and rats identified axonal degeneration as the primary pathological process.¹⁰

As with other mitotic spindle inhibitors, vincristine results in neurotubule breakdown, which is believed to disrupt axonal transport and lead to axon degeneration. In support of this hypothesis, vincristine has been shown to decrease the rate of protein delivery via rapid axonal transport.¹¹

References are on page 498.

MYCOTOXIC PERIPHERAL MYELINOPATHY

Vervet monkeys developed demyelinating peripheral neuropathy, cardiac and skeletal myopathy, and hepatitis when their maize meal diet contained a pure isolate of the fungus *Diplodia maydis*.¹ Growth of this fungus on maize had proved toxigenic previously in livestock in South Africa. Signs of peripheral motor and sensory dysfunction included loss of fine motor control in the hands and feet, tremor, ataxia, paresis, and acral nociceptive loss. Motor nerve

conduction velocities were reduced, but denervation potentials were not recorded. Studies of various peripheral nerves by light and electron microscopy revealed demyelination of internodes around intact axons. Demyelination preceded the appearance of macrophages in and around the affected sheaths.

The pathogenesis of the demyelinating polyneuropathy in this mycotoxicosis was not determined. Speculations included reduced bioavailability of energy and alternations of the blood-nerve barrier.

References are on page 498.

COYOTILLO (BUCKTHORN) POLYNEUROPATHY

Coyotillo (buckthorn) (*Karwinskia humboldtiana*) is a shrub that grows in the southwestern United States and in Mexico, where it is known as tullidora or capulincillo.¹ The leaves and brownish black berries of this shrub have for many years been known to produce a form of flaccid paralysis called limber leg. Species reported to be affected by eating the fruit have included cattle, goats, sheep, hogs, horses, chickens, and human beings.^{1,2} The clinical findings seem to have been recorded best in experimental intoxications in which fruit or extracts have been fed to various animals, such as goats, cattle, sheep, chickens, and guinea pigs.^{1,3} The latent period between feeding and the onset of signs varies from several days to weeks, depending on the species and the feeding regimen (i.e., dosage level and rate of administration). Often the first sign recorded was hyper-reactivity to stimuli.^{3,4} Subsequent findings included muscle tremors, ataxia, hypermetria, hind limb weakness with hock flexion, forelimb weakness with carpal flexion, recumbency with inability to rise, and loss of the gastrocnemius and patellar reflexes.^{1,3} In some cases, there has been progression to dyspnea and death. Animals with less severe paralysis often experience considerable weight loss but recover gradually.

Electrodiagnostic studies in experimentally intoxicated goats have demonstrated a substantial reduction in nerve conduction velocity.³ In experimentally poisoned cats, there was electrical evidence of conduction block, and paralyzed muscles in the hind limbs had mechanical properties like those found after denervation.⁵

Most studies on the peripheral nerves in spontaneous and experimental cases of coyotillo poisoning have provided evidence of paranodal and segmental demyelination of the larger axons.^{2,5-9} Charlton and Pierce⁶ followed the progression of lesion development in the peripheral nerves of intoxicated goats. The first change noted was Schwann cell swelling. As this swelling increased, there was widening of the nodes, and longitudinal clefts developed in the myelin sheath. Teased-nerve studies after systemic intoxication⁶ and intraneural injections⁹ revealed widening of the nodal gap and segmental demyelination. Wallerian degeneration was also observed in long motor nerves, where it involved the distal portions of larger axons.⁷

It has been suggested that this axon degeneration occurs secondary to a primary toxic effect on Schwann cell metabolism.^{2,8,9} More recent in vitro studies on buckthorn toxicity using mice spinal cord-dorsal root cultures, however, revealed a primary toxic effect upon the axon. The observed ultrastructural changes (e.g., widened periaxonal spaces, margination of axonal microtubules and other organelles, and central axonal concentration of neurofilaments) were thought to be consistent with a defect in axonal transport.¹⁰ A primary effect on peripheral axons also would be consistent with the changes that occur in the CNS of intoxicated goats.¹¹ In the CNS, swollen and degenerating axons have been found in both the cerebellum and spinal funiculi. Moreover, these central axonal changes may explain the hypermetria and ataxia that have been seen early in the course of buckthorn intoxication.

References are on page 498.

Autonomic nervous system

DISORDERS OF THE AUTONOMIC NERVOUS SYSTEM

Diseases of the autonomic nervous system (dysautonomia) are well recognized in humans, but few comparable syndromes are described in animals.¹ Grass sickness in the horse and feline dysautonomia (Key-Gaskell syndrome) qualify, however; curiously, both conditions occur mainly (but not exclusively) in the United Kingdom. **Grass sickness** presents as a peracute to chronic alimentary disturbance of horses kept at pasture (hence its name). All equidae including horses, donkeys, and zebras are susceptible.² The clinical presentation is of gastrointestinal stasis, which may

be partial or complete. Peracute cases present in shock and collapse with gastric refluxing and imminent death. Acute, subacute, and chronic forms are also recognized, the last with vague, intermittent signs of colic and alimentary disorder that may last for months. There is no definitive clinical diagnostic procedure,³ and the diagnosis depends upon the recognition of changes in the autonomic ganglia, particularly the coeliac-mesenteric, stellate, thoracic sympathetic chain, ciliary, cranial and caudal cervical, the craniospinal sensory ganglia, and selected nuclei in the CNS.

Lesions in the autonomic ganglia occur with the greatest regularity, and decades of experience have given them di-

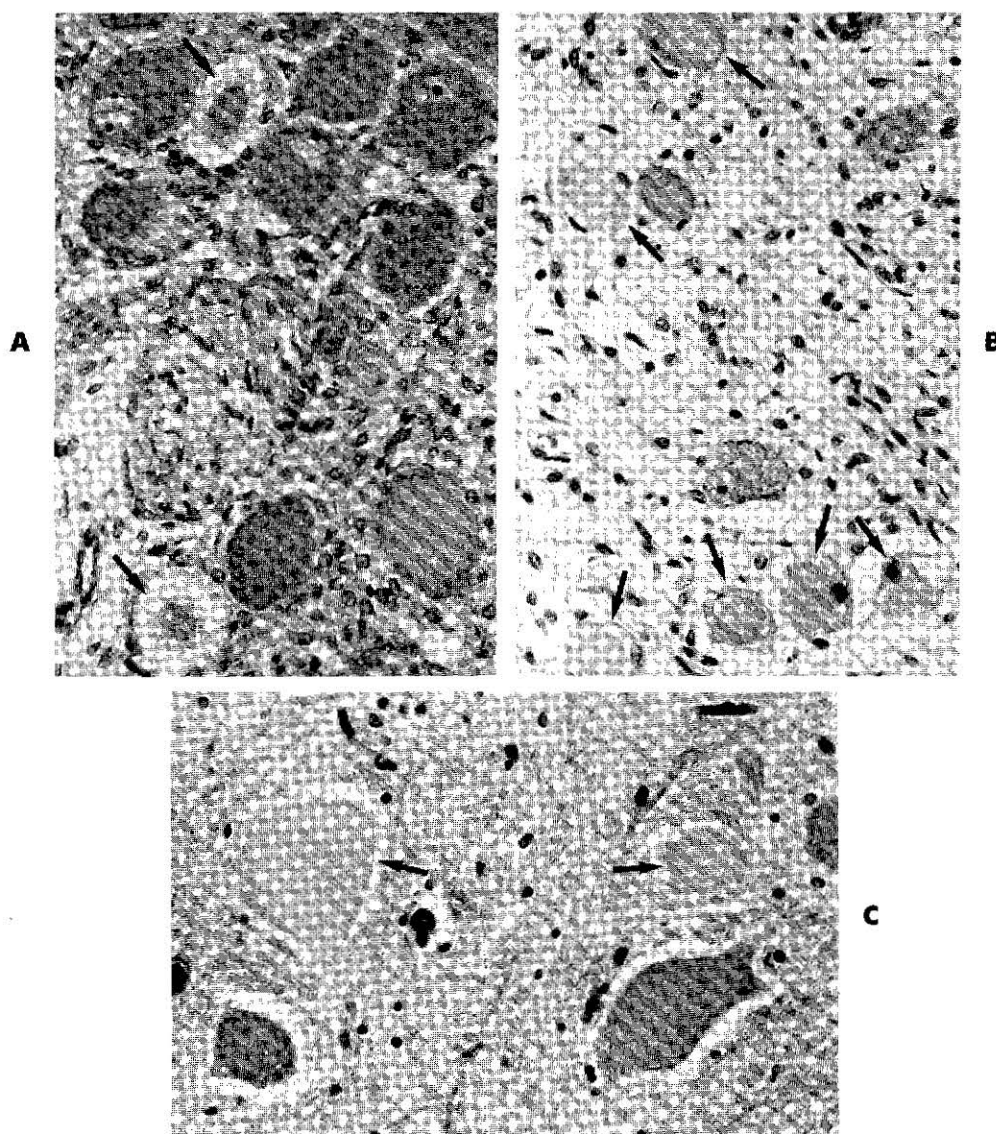


Fig. 7-36. Dysautonomia. **A**, Horse. Two intensely eosinophilic and peripherally vacuolated neurons (arrows) in an abdominal ganglion. **B**, Dog. Many neurons are degenerate (arrows), and the ganglion is depleted. (H&E, $\times 350$.) **C**, Dog. Swollen chromatolytic neurons (arrows) in spinal cord ventral gray column. (H&E, $\times 350$.)

agnostic specificity.⁴ The pathologist must be cautious when examining the neuronal population of this tissue as the Nissl bodies are normally dispersed to the periphery of the cell. The earliest recognized alteration is a chromatolysis of the neuronal perikaryon, this dissolution of the Nissl substance imparting an intense eosinophilia to the cell that may also contain multiple fine vacuoles (Fig. 7-36, A). The nucleus progressively contracts, and its pyknotic remains come to lie at the cell margin. In subacute to chronic cases, neuronal loss and satellite cell proliferation are more striking. Similar changes afflict neurons of several nuclei: the oculomotor, facial, vestibular, and dorsal motor nucleus of the vagus, accessory cuneate, and nucleus ambiguus, as well as the

intermediolateral and ventral gray column neurons in the spinal cord.^{5,6} Immunocytochemical studies of neuronal lesions in the autonomic ganglia indicate abnormalities of cytoskeletal and cytoplasmic proteins such as neurofilament and tubulin.⁷ Lesions are found in the dorsal root ganglia and the submucosal and myenteric ganglia of the alimentary tract, which show abnormalities of enteric peptides with diminished expression of substance P, vasoactive intestinal peptide, and others.^{8,9} Levels of plasma adrenalin, noradrenalin, and cortisol are elevated,^{10,11} suggesting sympathetic hyperactivity in affected horses.

The etiology is unknown but is thought to be a neurotoxin. Intraperitoneal inoculation of ponies with whole

blood, plasma, or serum from horses with acute grass sickness induces typical lesions in the recipients, although strangely no evidence of disease has been observed.^{12,13} The putative neurotoxin elutes in the plasma fraction of molecular weight 30,000 or greater. The important observation of similar lesions in the autonomic ganglia of sick hares, in the same district where cases of grass sickness have occurred,¹⁴ supports the hypothesis of an environmental, probably food-borne toxin.

Feline dysautonomia, an apparently new syndrome in the cat, was first reported by Key and Gaskell from Bristol, England, in 1982.¹⁵ This disorder has occurred in almost epidemic proportions in domestic cats in the United Kingdom and Ireland. Sporadic cases have been observed in Scandinavia and continental Europe and a few in the United States, the latter including both cats imported from Europe and indigenous animals.^{16,17} Disease is seen in cats of all ages, most commonly young adult domestic shorthaired types. There is no sex predisposition. In most cases, the onset of disease is acute, over 48 to 72 hours, although it may be insidious.¹⁸ The English experience with numerous cases has facilitated the recognition of 15 to 20 common clinical features,^{19,20} of which pre-eminent are dilated, non-responsive or poorly responsive pupils, prolapsed nictitating membranes, megaesophagus and regurgitation, dry nasal and oral mucosae, dysphagia, diminished tear production, constipation, and bradycardia. Affected cats are typically depressed, anorectic, dehydrated, and wasted. The majority of clinical signs reflect parasympathetic or sympathetic dysfunction, particularly the former.¹⁸ Some features, such as loss of anal sphincter function or proprioceptive deficits, are nonautonomic in origin. Therapy is largely supportive but some medications used in the treatment of human dysautonomias have been administered. In approximately 75% of affected cats, death has occurred or euthanasia is performed following a course of a few weeks to over 12 months.

Comprehensive studies of the light and ultrastructural changes in this disease have been reported.²⁰⁻²² At necropsy, the body is emaciated, with hard feces in the large bowel. Megaesophagus involving a segment or all of the esophagus is common. Autonomic ganglia, both sympathetic and parasympathetic, are consistently and uniformly affected. Celiac, mesenteric, and superior cervical ganglia have frequently been examined. Changes in somatic sensory ganglia (dorsal root ganglia, jugular) are found with lesser frequency and are typically milder than those in the autonomics. Early changes, observed in cats affected for a week or less, are a form of neuronal chromatolysis with loss of Nissl flakes

and diffuse cytoplasmic eosinophilia, swelling and then shrinkage of the cell, and an eccentric pyknotic nucleus. There is a progressive neuronal loss attended by satellite cell proliferation and light fibrosis; these features predominate in cats affected for 2 weeks or more. Typically, a few remaining, apparently normal, neuronal cell bodies can be found. Affected neurons in the sensory ganglia are much less common and involve the smaller cell population. In severe cases, certain populations within the CNS are affected including the oculomotor, trigeminal, facial, dorsal nucleus of the vagus, hypoglossal, nucleus ambiguus and the intermediolateral and ventral gray columns in the spinal cord. Within the CNS, chromatolytic neurons and neuronophagic nodules about shrunken cell bodies are observed, accompanied by a light gliosis and a trickle of mononuclear inflammatory cells.

The ultrastructural basis for this demise of neurons is a progressive disruption, degranulation, and vacuolar change in the rER, which harbors a flocculent material within its cisternae. Golgi complexes disappear, and the cytosol contains many autophagic vacuoles, dense bodies, and stacks of proliferated smooth endoplasmic reticulum. Concurrent nuclear changes are found: *The nuclear envelope is crenated, the nucleolus becomes condensed and dissociated into its subunits, and nuclear chromatin is clumped.* Degenerative changes are found in axons in the autonomic chain; they are swollen with tubulovesicular arrays, disorganized neurofilaments, and collections of mitochondria. Schwann cell proliferation (bands of Büngner) accompanies this axonal degeneration.

The etiology of this novel feline syndrome is unknown, despite exhaustive epidemiological investigations. Feline dysautonomia does not appear to be contagious insofar as multiple cat populations most commonly experience only single cases of the disorder. An infection, perhaps subclinical in most cats, could be considered. Alternatively a neurotoxin with a particular tropism for neurons of the autonomic ganglia is envisaged. This putative neurotoxin spares the satellite cells and involvement of somatic neurons occurs with much lower frequency, as judged by clinical deficits and pathological alterations.

Dysautonomia has been recognized rarely in dogs (Fig. 7-36, B and C).²³⁻²⁵ These observations, largely from the United Kingdom, doubtless reflect the experience gained by clinicians in that country with the feline disorder. Dysautonomia may occur more widely in the canine population, although probably on a sporadic basis.

References are on page 498.

Neoplasia and the peripheral nervous system

PARANEOPLASTIC NEUROPATHY

Paraneoplastic neuropathies have been described in association with various malignancies in the dog. The peripheral neuropathological changes involve multiple nerves and are a remote rather than a direct effect of the malignancy. In 16 of 21 dogs with malignant neoplasms, Braund and others¹ found peripheral nerve lesions that were in excess of the norm for age-related changes.^{2,3} Surprisingly, none of the 16 animals had clinical signs of peripheral nerve disease despite substantial lesion development. The pathological studies in this series were based on teased-fiber preparations of the common peroneal and ulnar nerves. In these preparations, demyelinating and remyelinating changes, in general, were more frequent than axon degeneration. The myelin and axon changes were similar to those described in normal older dogs,^{2,3} but they occurred with greater frequency.

Neuropathies or neuromyopathies of presumed paraneoplastic origin have also presented with clinical signs. Dyer and others⁴ performed thorough clinical, neurological, and pathological investigations on two older dogs with diffuse paresis, hypotonia, muscle wasting, and depressed reflexes. Although both dogs had neoplasms (a leiomyosarcoma in one and a hemangiosarcoma in the other), the authors were reluctant to attribute the observed distal axonopathy in the peripheral and recurrent nerves to a paraneoplastic etiology because both dogs were also hypothyroid. The contributions of the neoplasms and hypothyroidism to the peripheral neuropathies in these animals could not be defined. Presthus and Teige⁵ recorded right hind lameness and facial weakness in a 6-year-old dog with lymphosarcoma of the stomach. Examination of the femoral and facial nerves in this case revealed myelin sheath loss with preservation of axons. Griffiths and other investigators⁶ found evidence in two dogs for both direct and remote effects of malignancies on the PNS. In one dog, an undifferentiated sarcoma invaded the L4 to S1 spinal roots on the right, and in the second animal a fibrosarcomatous mass in the right axilla infiltrated the brachial plexus. In both dogs, however, there also appeared to be remote clinical and pathological effects. Both animals had delayed conduction velocities in peripheral nerves far removed from the direct effects of the tumors. The remote changes were largely demyelinating in the peripheral nerves of the first animal but involved both myelin and axons in the second. No inflammatory infiltrates were seen in the nerves of either animal. Cardinet and Holliday⁷ in an extensive survey of neuromuscular disease identified two dogs in which polyneuropathy occurred in association with neoplasia. This survey, which was based on muscle biopsies,

revealed neuropathic or denervation changes (e.g., angular atrophy of types I and II muscle fibers) in two 8-year-old dogs with adenocarcinoma.

Diagnosis of paraneoplastic neuropathy can be further complicated by use of chemotherapeutic agents that in themselves induce peripheral neuropathological changes (e.g., doxorubicin, vincristine). In this regard, a 12-year-old dog with multiple lymphoid neoplasms developed hind limb weakness and ataxia after a 16-week course of vincristine treatment. In accordance with electrodiagnostic findings, a peroneal nerve biopsy revealed extensive degeneration of myelinated axons. Discontinuation of the vincristine for 2.5 months brought about regression of signs of neuropathy and fewer abnormalities on a peripheral nerve biopsy specimen.⁸

In humans, an association between malignancies and periphery neuropathy, independent of metastases, has been established since 1948.⁹ Clinical and subclinical varieties have been recognized. Both sensory and sensorimotor types of carcinomatous or paraneoplastic neuropathy have been identified. The sensorimotor type is more prevalent. Pathological studies of the sensory form of carcinomatous neuropathy have revealed a ganglioradiculitis¹⁰⁻¹² that appears comparable to the canine ganglioradiculitis described in this chapter except for concurrent CNS inflammatory involvement in some human patients. The sensorimotor form of carcinomatous neuropathy has been characterized pathologically by a reduction in the number of myelinated axons in the peripheral nerves. This reduction has been associated with axon degeneration, which was the most prevalent abnormality.⁹ Various forms of peripheral neuropathy have also been associated with lymphomas and other reticuloses in humans.¹³

It would seem that greater clinical and pathological definition of the canine paraneoplastic neuropathies will be needed before nosological limits can be defined and before contrasts and comparisons can be made with the forms of human carcinomatous neuropathy or neuropathy associated with lymphoma.^{9,13} The pathogenetic mechanisms thought to operate in paraneoplastic neuropathy in humans have been suggested for the canine disorders as well. These have included diverse metabolic factors, nutritional deficiency, vascular changes, endogenous or exogenous toxic factors, viral infections, or immunological disturbance.^{9,13}

References are on page 499.

NEUROPATHY ASSOCIATED WITH INSULINOMA

Occasionally **insulinomas in dogs** have been associated with clinical or subclinical peripheral neuropathy.¹⁴ The numbers of recorded cases are few. Chrisman¹ in a study

of 10 dogs with insulinoma, had one 9-year-old mongrel with a 4-month history of weakness that culminated in recumbency and inability to rise. A diagnosis of polyneuropathy was supported by delayed motor nerve conduction velocities and electrical evidence of muscle denervation in the form of fibrillations and positive-sharp waves. Polyneuropathy in a 12-year-old Irish Setter with a functional β -cell tumor was manifest by weakness, loss of patellar reflexes, muscular atrophy, slowed proprioceptive reactions, and denervation potentials recorded in the muscles distal to the elbow and stifle.² Schrauwen's diagnosis⁵ of polyneuropathy associated with insulinoma in a 10-year-old Irish Setter was based on clinical findings of seizures, ataxia, tetraplegia, muscle atrophy, hypoglycemia, and elevated amended insulin:glucose ratio. In this case, no biopsy or necropsy was permitted. Braund with others³ described two dogs with insulinoma and subclinical neuropathy. In a 7-year-old Weimaraner with facial weakness and masticatory muscle atrophy, axon degeneration predominated in the facial nerve, but demyelinating and remyelinating changes were found in peripheral nerve samples. In a 12-year-old mongrel, with no obvious clinical signs of peripheral nerve disease, denervation potentials were recorded in some limb muscles. In peripheral nerve samples obtained at necropsy, demyelination and remyelination were encountered more often than axon changes. Axon degeneration, however, affected approximately 20% of fibers in the common peroneal nerve. Thus in dogs, the polyneuropathy associated with insulinoma seemed to consist of a mixture of changes: demyelination, remyelination, and axon degeneration. The pathogenesis of the polyneuropathy remains obscure. Suggested pathogeneses have included metabolic defects induced by hyperinsulinism, effects of hypoglycemia, or a paraneoplastic or indirect immunological effect of the pancreatic tumor.^{2,3}

In transgenic mice that develop functional islet cell adenomas as a consequence of simian virus 40 oncogene expression in β cells, the onset of a generalized peripheral neuropathy was correlated with hyperinsulinemia and hypoglycemia.⁶ Although the initial site of damage was not determined, the neuropathy was characterized by preferential degeneration of large myelinated axons. Studies in streptozocin-induced diabetic mice also disclosed a close correlation between insulin-induced hypoglycemia and degeneration of peripheral myelinated axons.⁷ Similarly in humans, neuropathy in association with insulinoma has been designated as a "hypoglycemic neuropathy." This relatively rare, sensorimotor neuropathy with loss of large myelinated axons was suspected to have its etiology rooted in glycopenia rather than hyperinsulinism.⁸ In humans with insulinoma, however, it has not been determined if the neuromuscular symptoms result from peripheral neuropathy or from lesions of the anterior horn cells and neurons of the spinal ganglia.⁹

References are on page 499.

TUMORS OF THE PERIPHERAL NERVOUS SYSTEM

Tumors of the PNS are uncommon in most of the domestic and laboratory animal species. As a clinical entity, they are numerically important only in the dog. The nomenclature of these tumors is exceptionally confusing. Numerous designations have been used in the medical and veterinary literature, including schwannoma, neuroma (sometimes qualified as acoustic neuroma), neurinoma, neurilemmoma, neurofibroma, and neurofibrosarcoma. These terms, entrenched in human neuropathology, have been borrowed for use in animal pathology, often without a clear understanding of how they are used, and what they imply, in humans. We must not lay all the blame for this confusion with the veterinary pathologist, however, as in human medicine there is not complete uniformity in the way these tumors are named. It may be useful to begin this section by providing a framework for the use of this nomenclature, as is most commonly practiced in humans. It will be clear that the designation neurofibroma should perhaps be limited to a specific human neoplasm.

Schwannomas and neurofibromas are considered to be distinct entities by most human neuropathologists. **Schwannomas** of humans are tumors of Schwann cells; they are usually solitary and benign and rarely recur if completely excised. Many occur in spinal nerve roots, cranial nerves, or elsewhere in the PNS. Because schwannomas of the eighth cranial nerve are common in people, accounting for perhaps 60% of human schwannomas, they have acquired the separate designation of acoustic neuroma. This nomenclature is pathologically imprecise, as neuroma is a term for a non-neoplastic swelling of a nerve, such as an amputation neuroma.

Another designation often used synonymously with schwannoma is neurilemmoma (also spelled neurolemmoma). Neurilemma literally means "nerve membrane, sheath, or covering," as we use this suffix in plasmalemma or sarcolemma, and so a neurilemmoma is a tumor of the cells that ensheath or cover a nerve fiber. In naming a tumor, it is decidedly preferable (where possible) to use a term that specifies the presumed cell of origin of the neoplasm, such as schwannoma for a Schwann cell tumor and perineurioma for a tumor of perineurial cells.

Macroscopically, schwannomas are discrete, encapsulated, and tend to displace the unaffected portion of the nerve trunk. Microscopically, they contain two intermingling patterns of Schwann cell growth referred to as **Antoni type A** and **Antoni type B** patterns. Antoni type A areas consist of sheets and fascicles of spindle-shaped Schwann cells with fusiform nuclei (Fig. 7-37). Characteristic patterns of growth are parallel arrangements of these nuclei, giving a palisaded pattern. Antoni type B areas are looser with fewer cells, having smaller, round dark nuclei and spaces between the cells. It has been proposed that Antoni type B regions are areas of degeneration within the neo-

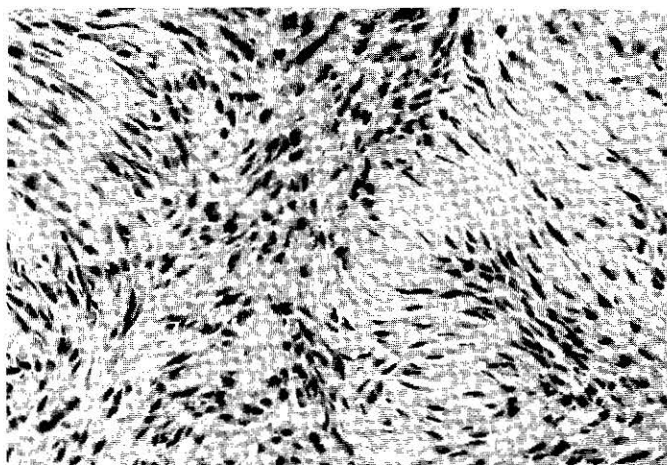


Fig. 7-37. Schwannoma, human. Tumor of eighth cranial nerve. Antoni type A pattern. (H&E, $\times 350$.)

plasm.¹ A second configuration results in the formation of **Verocay bodies** in which two chains of nuclei are arranged at the margins of a central cytoplasmic mass. Schwannomas usually do not contain axons. In human schwannomas, a variety of secondary features are recognized, including vascular ectasia and hyalinization, xanthomatous change, fibrosis (following tumor infarction), and pleomorphism of nuclei. All of these features are helpful in making a distinction from neurofibroma.

Ultrastructurally, schwannomas contain variably well-differentiated Schwann cells, each coated by a continuous basal lamina that contains type IV collagen.² They bear 10-nm intermediate filaments and sparse pinocytotic vesicles. Extracellular long-spaced collagen ("Luse bodies") is a characteristic feature. These neoplastic cells may be stained immunocytochemically with antisera to S-100 antigen, Leu 7, and vimentin.^{3,4} In contrast, myelin-specific proteins such as myelin basic protein and P₂ protein were not found to be expressed by Schwann cell neoplasms.⁵

As well as classical schwannomas, variants are recognized, including cellular schwannoma,^{6,7} pseudoglandular schwannoma,⁸ and melanotic schwannoma.^{9,10}

So far, so good. It is in the concept of the neurofibroma that problems arise. **Neurofibromas** in humans are also tumors of Schwann cells, but they are admixed with other cell types. These other components are often stated to be fibroblasts but probably also include perineurial cells.¹¹⁻¹³ Neurofibromas occur in the skin, along deep nerve trunks, associated with abdominal organs, or retroperitoneally. Single cases are recognized but are uncommon. Most are multiple and occur as part of the spectrum of **neurofibromatosis type 1** (von Recklinghausen's disease, neurofibromatosis), a common, dominantly inherited, multisystemic human disorder that in its spectrum has no parallel in the natural diseases of animals. Neurofibromatosis type 1 (NF1), which

has been assigned to chromosome 17, is a mixed syndrome of dysplastic development with malformations, hamartomas, heterotopias, and multiple organ neoplasia. Patients with NF1 may have CNS and skeletal malformations such as polymicrogyria and kyphoscoliosis, multiple hyperpigmented skin lesions referred to as café-au-lait spots, multiple neurofibromas, and other tumors of the PNS, CNS, and other organs. Diagnosis is established by identifying two or more features of a standard list of stigmata.¹⁴ A mouse model for human neurofibromatosis has been contrived,¹⁵ employing transgenic animals that carry the tat gene of human T-lymphotropic virus type 1.

Neurofibromas are poorly encapsulated and, rather than bulging from a nerve trunk (as do schwannomas), involve it diffusely in a plexiform pattern, producing a bulbous enlargement of the whole trunk. Skin masses are rubbery, pedunculated nodules. Histologically, neurofibromas are a loose, mixed pattern of nerve fibers, Schwann cells, fibroblasts, perineurial cells, and sometimes also mast cells. The demonstration of axons within the tumor is important in separating neurofibromas from schwannomas. The matrix may be densely collagenous or loose and mucoid. Ultrastructural findings are of varying proportions of mature Schwann cells, fibroblasts laden with rough endoplasmic reticulum, and perineurial cells with discontinuous basal lamina and numerous pinocytotic vesicles at the plasmalemma. Immunocytochemical findings largely reflect the Schwann cell component of the tumor.^{3,4}

In NF1,¹⁶ transformation of neurofibroma to a malignant neurofibrosarcoma with increased cellularity, cellular pleomorphism, and a malignant behavior is well recognized. Furthermore, other primary tumors may subsequently arise in the patient, including gliomas, meningiomas, and schwannomas, the last most frequently with bilateral eighth nerve involvement. Thus if a diagnosis of neurofibroma is made, it is imperative to establish whether the tumor is part of the expression of NF1, as this has implications for the patient and for the family who may be carriers of the gene. Solitary neurofibromas, unassociated with NF1, do occur in humans, but are much less common. Hence, from this synopsis, it can be seen that although the term neurofibroma has been applied to many PNS tumors of animals, we may have borrowed this term from human neuropathology naively, perhaps ill-advisedly, and without a recognition that neurofibromas are mixed tumors and that they most commonly arise in patients with a complex, dominantly inherited disorder of growth.

In humans, it has recently been proposed that there is a benign peripheral nerve tumor derived from the perineurial cell, the **perineurioma**.¹⁷⁻¹⁹ Immunocytochemically, perineurial cell tumors are found to express epithelial membrane antigen, in contrast to schwannomas, which are positive for Leu 7 and/or S-100 protein.^{13,20}

In the **dog**, tumors of the PNS occur in the cranial and spinal nerves. Some have been designated neurofibromas

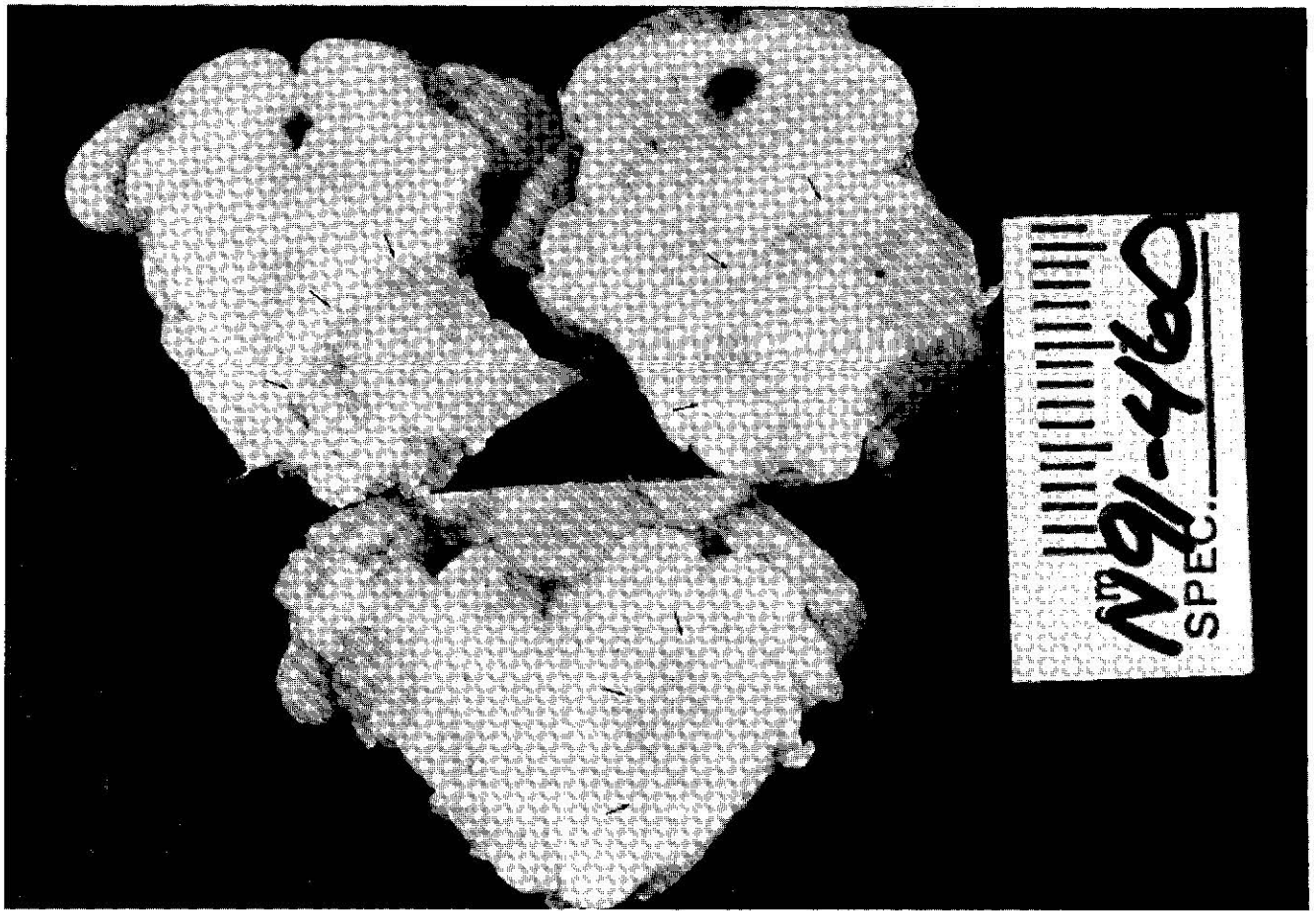


Fig. 7-38. Malignant peripheral nerve sheath tumor of trigeminal nerve, dog. Tumor compresses brain stem (arrows).

or neurofibrosarcomas,^{21,22} based on the classification of Fankhauser, Luginbühl, and McGrath.²³ These authors found neurofibromas to be rich in connective tissue components (although sometimes containing schwannoma-like areas) and so proposed an origin from endoneurial and perineurial cells. Doubtless mesenchymal tumors, derived from endoneurial and epineurial fibroblasts, occur in the PNS; fibrosarcomas of cranial nerves in two dogs have been reported.²⁴ Others have studied PNS neoplasms in the dog and have designated them schwannomas,²⁵ which is a term preferable to neurofibroma. Unfortunately, many PNS tumors in the dog are anaplastic and do not demonstrate the classical light microscopic features of human schwannomas, which have been previously detailed. In animals, such features are best seen in schwannomas in cattle. Poorly differentiated PNS tumors are best designated malignant peripheral nerve sheath tumors.

In the dog, tumors of the cranial nerves most frequently involve the trigeminal nerve. Neurogenic atrophy of the muscles of mastication is a common result, as well as loss of facial sensation. Brain stem signs follow the compressive

effects of the tumor intracranially (Fig. 7-38). Many canine PNS tumors arise within the caudal cervical nerve roots, most often C6 to C8,²⁵ but these brachial plexus tumors may also involve T1 and T2. Clinically, there is a slowly progressive course of unilateral forelimb lameness, pain, and muscle atrophy that may be neurogenic and/or due to disuse.^{26,27} Compression of the cranial thoracic spinal cord by the invasive tumor may produce Horner's syndrome, with mild upper motor neuron and general proprioceptive signs in the ipsilateral pelvic limb. Invasion beyond the spinal cord into the thorax²⁸ is most unusual. Surgical treatment usually requires amputation of the forelimb with the mass, but, with early diagnosis, successful excision of a C6 schwannoma has been reported.²⁹ In contrast, PNS tumors of the thoracic or lumbar segments tend to present more acutely, referable immediately to spinal cord compression. This pattern has been observed with tumors involving the forelimb but is rare.³⁰

Carmichael and Griffiths²⁶ have observed three tumors of soft tissues that, by extension, involved the brachial plexus. Two were sarcomas, while the third was a mixed

malignant tumor of the apocrine sweat glands; all metastasized to lung or local lymph nodes. In the more common intrinsic PNS neoplasm that arises within the brachial plexus, the typical finding at necropsy is grayish, fusiform thickening of several nerve trunks, sometimes with fusion into a common tumor mass (Fig. 7-39). Histologically, such cases vary from dense fascicles of Schwann cells with elongated nuclei and pale indistinct cytoplasm to more anaplastic forms (Fig. 7-40). Many canine PNS tumors are malignant as evaluated by both cytological criteria (anaplasia, abundant mitosis, necrosis) and biological behavior (invasion of adjacent tissues including, often, the spinal cord). In such cases discrimination of the cell of origin—whether schwannian, perineurial, fibroblastic, or other—is often impossible in routine sections. Many such tumors have been (arbitrarily) reported as malignant schwannomas or neurofibrosarcomas without definitive identification of the principal cell being possible. In such cases, the preferred designation of the neoplasm is **malignant peripheral nerve sheath tumor (MPNST)**,¹¹ to be modified if necessary when further studies (immunohistochemistry, electron microscopy, tissue culture, etc.) have been performed. In humans, MPNST may show varying patterns of differentiation, including rhabdomyoblastic, angiomatous, osseous, and epithelial patterns.^{31,32} We have observed differentiation to primitive cartilage, to bone, and to squamous epithelium with keratinization in canine MPNSTs, and Dahme and colleagues³³ have observed rhabdomyoblastic features in one (Fig. 7-41, A and B).

Most reports of these tumors in veterinary medicine describe only the conventional light microscopic findings. Dahme and colleagues³³ have studied a series of canine cranial and spinal nerve root tumors immunocytochemically. Of 13 tumors, 11 were diagnosed as neurinomas (schwannomas), and all were positive for S-100 antigen. Two tumors diagnosed as neurofibromas were S-100 neg-

ative. Ultrastructural studies of canine PNS tumors are rare. Vandeveld, Braund, and Hoff³⁴ observed fibroblastic features in two tumors, which they named central neurofibromas. Electron microscopic details have been provided for two 2-year-old dogs with melanotic schwannomas (Fig. 7-41, C).³⁵ This rare variant is also recognized in humans.⁹ Tumor cells, resembling Schwann cells, also contain cytoplasmic premelanosomes and mature melanosomes, this dual phenotype presumably reflecting the common origin of Schwann cells and melanocytes from the neural crest.

PNS tumors are rarely reported in the **cat**. Similar to a case described by Zaki and Hurvitz,³⁶ we have observed a malignant schwannoma in a mature cat that presented with progressive pelvic limb ataxia. At necropsy, a 1-cm-long, gray, extradural mass was found at the T13-L1 junction on the left side of the spinal cord. The tumor had compressed the spinal cord and had eroded through the T13 vertebral body, extending into adjacent musculature. Microscopically, the mass, involving the dorsal spinal root, contained extensive areas of densely packed epithelioid cells with some fusiform patterns of growth. Blood vessels had hyalinized walls. Neoplastic cells were positive for S-100 antigen, and ultrastructural examination revealed epithelioid Schwann cells with characteristic features (Fig. 7-42).

Tumors of the PNS are well recognized in **cattle**. Most do not cause clinical disease but are identified as incidental findings in old cows sent to slaughter. Because multiple nerves may be affected, this condition has been called neurofibromatosis with analogies to the human disorder. The preferred diagnosis is multiple (multicentric) schwannoma.²⁷ In cattle, there is a predilection for involvement of the autonomic nervous system, and tumors are particularly found in the epicardial plexus (Fig. 7-43, A), brachial plexus, mediastinum, intercostal nerves, and thoracic sympathetic ganglia.^{38,39} Intracranial involvement is typically vestibulocochlear, which invites analogies with the human

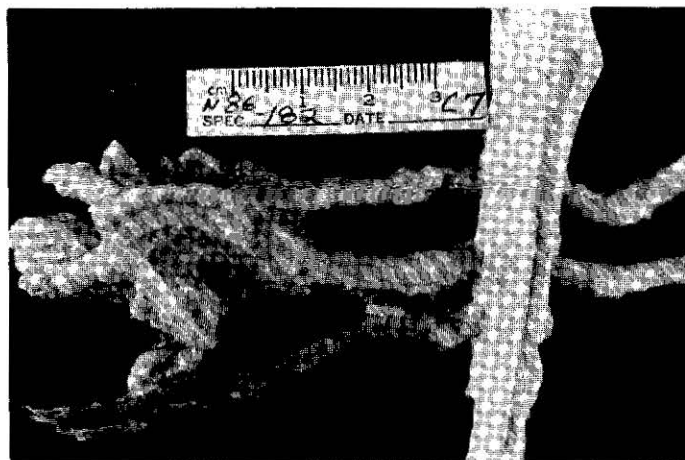


Fig. 7-39. Malignant peripheral nerve sheath tumor, dog. Brachial plexus.

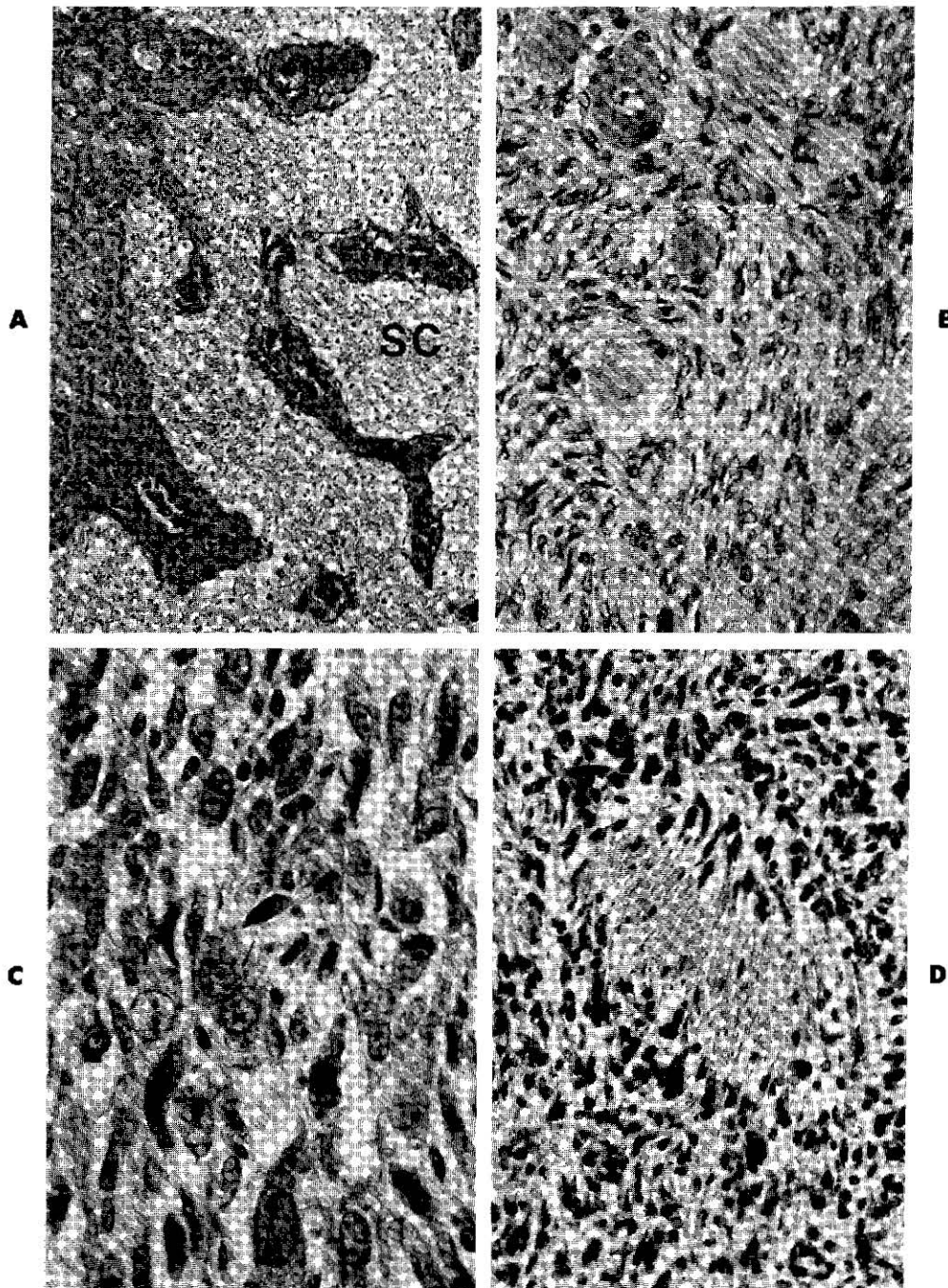


Fig. 7-40. Malignant peripheral nerve sheath tumor, dog. **A**, Extramedullary tumor infiltrates along blood vessels into the spinal cord (SC). Often these vessels show a hyaline change. (H&E, $\times 140$.) **B**, MPNST infiltrates spinal ganglion. (H&E, $\times 350$.) **C**, Pleomorphism in MPNST. Note binucleate cell (arrow). (H&E, $\times 560$.) **D**, Verocay body. (H&E, $\times 350$.)

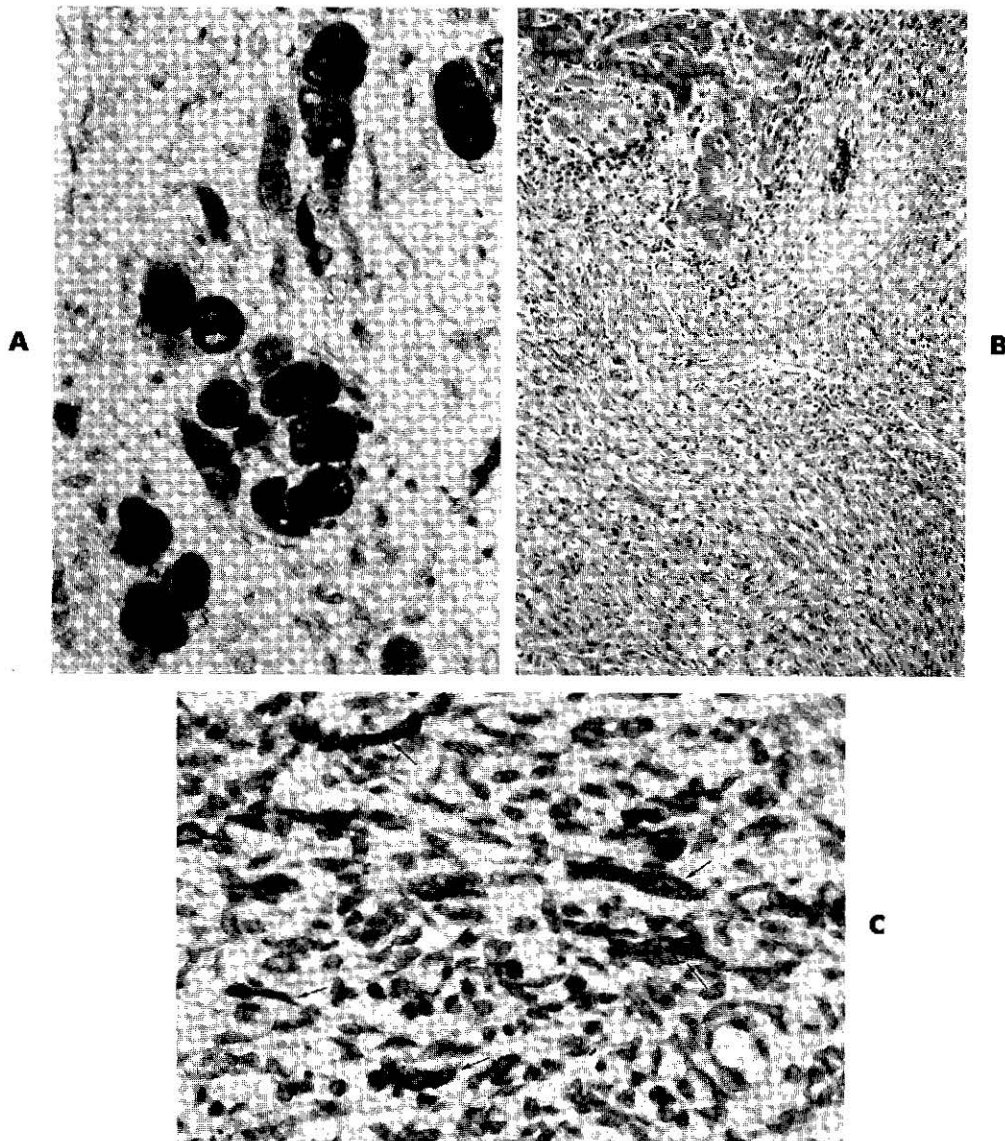


Fig. 7-41. Malignant peripheral nerve sheath tumor. **A**, Triton tumor, human. Rhabdomyoblastic differentiation. (Myoglobin immunocytochemistry, $\times 350$.) **B**, Dog. Osteosarcoma arising within MPNST. (H&E, $\times 140$.) **C**, Dog. Melanocytic Schwannoma. Many cells (*arrows*) contain melanin pigment. (H&E, $\times 560$.)

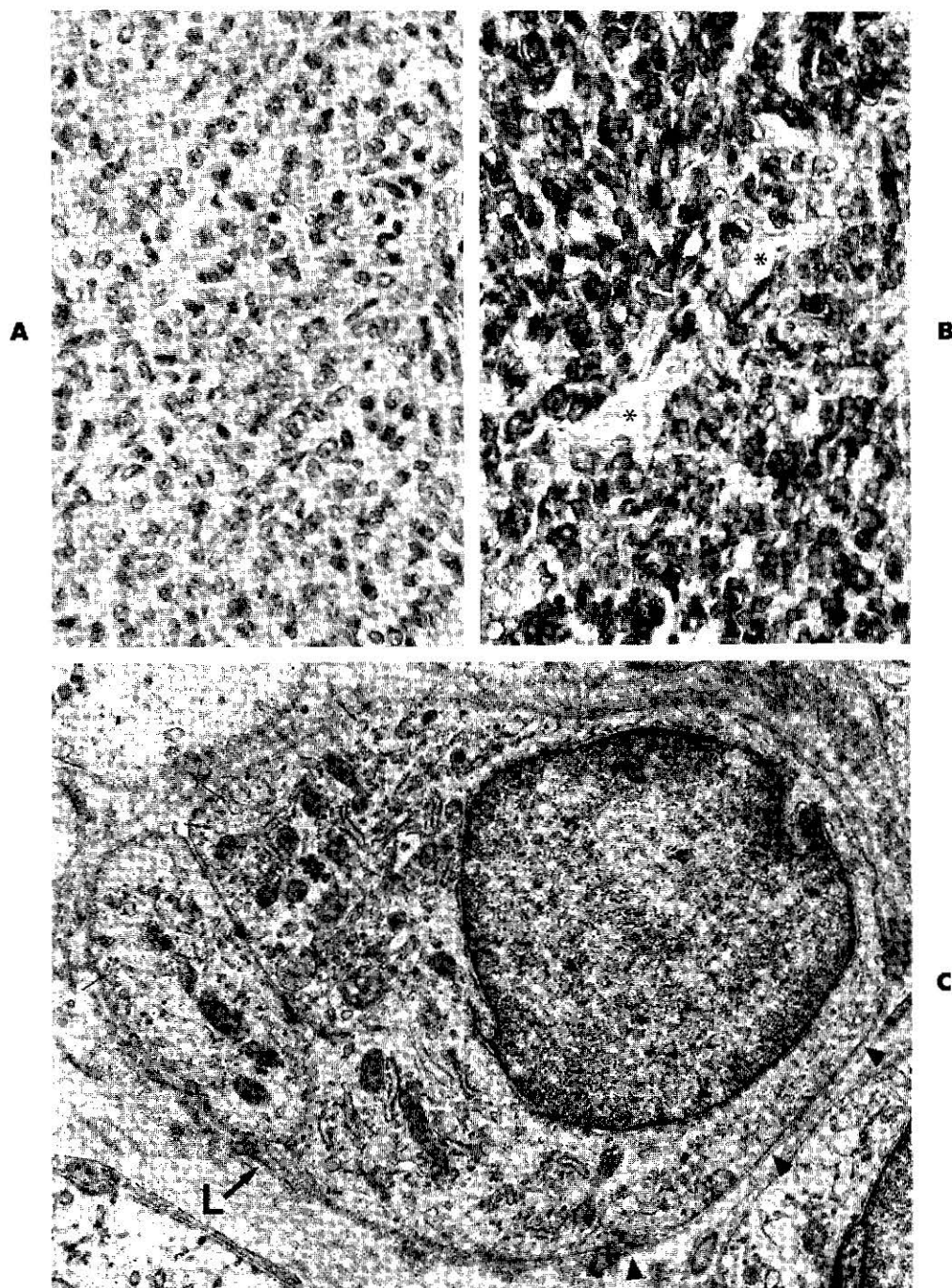


Fig. 7-42. Malignant schwannoma, cat. **A**, Microscopic appearance: somewhat epithelioid cells. (H&E, $\times 140$.) **B**, Same field stained for S-100 antigen, which is expressed in both nucleus and cytoplasm. Unstained blood vessel (*asterisk*) traverses the field. ($\times 560$.) **C**, Ultrastructure of the schwannoma. The plasmalemma has a continuous basal lamina (*arrowheads*), and there are scattered pinocytotic vesicles (*arrows*). Note extracellular Luse body (*L*)—long-spaced collagen—a characteristic feature of schwannoma. ($\times 17,000$.)

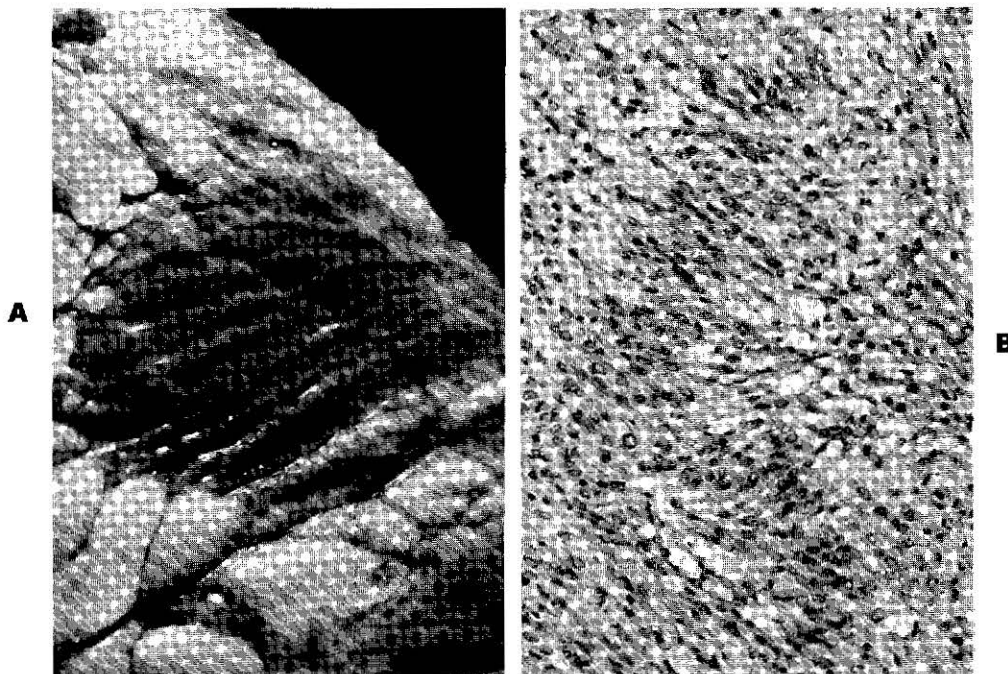


Fig. 7-43. Schwannoma, cow. **A**, Enlargement of nerve plexus in epicardial fat. **B**, Palisading pattern in bovine schwannoma. (H&E, $\times 225$.)

“acoustic neuroma.” Affected nerve tracts are grossly thickened, firm, nodular, and whitish gray. Some are mucoid. Microscopically, there are several features of human schwannomas with Antoni type A areas, nuclear palisading (Fig. 7-43, *B*), and Verocay body formation. Blood vessels with hyalinized walls, a feature of the human tumor, are also observed. These bovine tumors are particularly confusing as they may show a nodular or plexiform pattern, a feature associated with neurofibroma. However, plexiform patterns in human schwannomas, although rare, are recognized.⁴⁰⁻⁴² Canfield has studied these tumors from cattle ultrastructurally and in tissue culture^{43,44} and has demonstrated that they have a significant schwannian component. A few have been studied immunocytochemically, and S-100 expression has been found.^{37,45} As Luginbühl, Fankhauser, and McGrath⁴⁶ have suggested, these tumors of cattle share some similarities with human neurofibromatosis, but too close a parallel is unwarranted.

A unique disorder affecting spotted Slovakian calves was observed on one farm in the progeny of a single bull.⁴⁷ Reported in 1978 as congenital neurofibromatosis, affected calves had progressively enlarging tumors in the skin and nerves of the head. The cellular composition was said to be fibroblastic with extracellular collagen fibrils, but some features described suggest a possible Schwann cell or perineurial cell component.

In the laboratory animals, spontaneously arising schwannomas have been described in the **rat**.⁴⁸ Administration of carcinogens such as ethylnitrosourea to pregnant rats will induce schwannomas in their progeny.⁴⁹ One such tumor,

produced by the administration of methylacetoxymethyl nitrosamine, showed areas of transition from schwannoma to granular cell myoblastoma.⁵⁰ Granular cell tumors arising in the PNS have been observed in humans^{51,52} and are taken to support the origin of some granular tumors from Schwann cells.

It is interesting to note that schwannomas have been observed in **fish**.⁵³ In Japan, these have occurred in Coho Salmon, which are imported as eggs and raised locally. Fungicides, used to sterilize the eggs, have been investigated as the possible basis for these tumors.⁵⁴ Histologically, they show classical Antoni type A and type B patterns.

Peripheral tumors of **neuronal** origin are rare in animals. Most have been seen in cows, dogs, and rats. Neuroblastomas and ganglioneuromas, presumptively derived from the sympathetic ganglia, are observed in the retroperitoneum and mediastinum.^{55,56} Adrenal neuroblastomas and ganglioneuroblastomas are seen in cattle⁵⁷⁻⁵⁹ and rats,⁶⁰ and sometimes disseminated ganglionic tumors of uncertain origin are encountered.⁶¹ Intestinal ganglioneuroma, presumably derived from the enteric nervous system, is reported in the dog, pig, and cat.⁶²⁻⁶⁵ Esthesioneuroblastoma (olfactory neuroblastoma) is a controversial and uncommon human neoplasm that arises in the roof of the nasal cavity or nasal sinuses. Some resemble classical neuroblastomas; others reveal neuroendocrine features.⁶⁶ Very few esthesioneuroblastomas have been described in animals. They have been recorded in the cat^{67,68} (where an association with feline leukemia virus has been observed⁶⁹), dogs,^{46,70} a cow,⁷¹ and a horse.⁷² **Primitive neuroectodermal tumors** arising in

peripheral nerves are rare, highly malignant tumors that may show neuroblastic features. They are described in humans⁷³ but not animals.

Peripheral nerve involvement with neoplasms of non-neural origin is rare. **Marek's disease** is a herpesvirus-induced lymphoma of chickens that may affect the CNS, visceral organs, and peripheral nerves. The PNS lesions may be lymphomatous but in some circumstances have an inflammatory nature with perivenular infiltrates of lymphocytes and macrophages and demyelination, similar to experimental allergic neuritis.^{74,75} In domestic animals, involvement of the PNS in cases of **myeloid or lymphoid neoplasia** must be rare, save for the sporadic occurrence of intradural spinal lymphoma in the cat or cow that may involve spinal roots. Two dogs with myelomonocytic leukemia, which affected several cranial and spinal nerves and their ganglia, have been reported.^{76,77} Fankhauser and associates⁷⁸ described a 14-year-old mare with lymphoma that involved the distal portions of several cranial and peripheral nerves. Feline lymphoma, involving several cranial nerves or the brachial plexus, has been described.³⁶

References are on page 499.

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INDEX

- A**
- Abbreviations, 502
- Aberdeen Angus cattle
cerebellar cortical abiotrophy in, 304
mannosidosis in, 226
parainfluenza in, 118
- Abiotrophy, 2
cerebellar cortical, 86, 301-305
neuronal, 300-307
- Abscess, 156-159
- Acanthamoeba castellanii*, 170
- Acid β -galactosidase, 230
- Acid hydrolases, 214
- Acid sphingomyelinase, 224
- Acidemia, hyperpipecolic, 214
- Acidophil adenoma, 383
- Acidosis, metabolic, 212
- Acoustic nerve radiculitis, 436
- Acoustic neuroma, 473
- Acremonium loliae*, 261
- Acrylamide intoxication, 421
- ACTH; *see* Adrenocorticotrophic hormone
- Actinobacillus equuli*, 156
- Actinomyces pyogenes*, 158
- Activator protein, 214
- Acute idiopathic polyradiculoneuritis, 424-427
- Addison's disease, 246
- Adenocarcinoma, 392
- Adenoma, 383
- Adenovirus vasculitis, 117, 118
- Adhesion molecules, 40
- Adrenocorticotrophic hormone, 382
- Adrenoleukodystrophy, 214, 281
- Adult polyglucosan body disease, 327
- Aedes*, 145
- Aerosol infection, 97
- Afferent nerve fibers, 410
- Afghan Hound, 283-284
- African swine fever, 126
- Agensis of corpus callosum, 72
- Aging, 49-55
degenerative myelopathy in, 319-321
encephalitis in, 110
myelin and, 406
- Aging pigment, 52
golden yellow, 7
- Agrostis*, 262
- Airedale, 301
- Akabane virus, 73, 84
- Akita, 116
- Alaskan Husky, 212, 213
- Alaskan Malamute, 441-442
- Alcohol fixation, 423
- Alexander's disease, 281, 282, 283
- Alkaloids, 261
- Alkylmercurial poisoning
central nervous system and, 254
peripheral nervous system and, 466-467
- Allergic neuritis, experimental, 421
- ALS; *see* Amyotrophic lateral sclerosis
- Alsatian dog, 316
- Alzheimer type astrocytes, 12, 210, 211
- Alzheimer's disease, 54-55
neurons in, 7
- Amaurotic idiocy, 234
- Amblyomma americanum*, 151
- Amblyomma* ticks, 150
- Amebic meningoencephalitis, 170
- Ameboid microglia, 21, 22
- p-Amino-benzenearsonic acid, 252
- Aminoacidopathies, 211
- Γ -Aminobutyric acid, 211
- Amphicytes, 412
- Amputation neuroma, 455-457
- Amylo-1,6-glucosidase, 232
- Amyloidosis, cerebrovascular, 54, 55
- Amyotrophic lateral sclerosis, 308
cytoplasmic inclusions in, 7
- Anaplastic astrocytoma, 363, 364, 368
- Anaplastic ependymomas, 375
- Anaplastic oligodendrogliomas, 372-373
- Anatomic megalencephaly, 74
- Ancillary procedures, 47-48
- Anemia, infectious, 146-148
immune complex formation in, 116
- Anencephaly, 68-69
- Anesthesia-related syndromes, 241-242
- Angioblastic meningioma, 359, 360
- Angiomas, 354
- Angiostrongylus cantonensis*, 162
- Angiotropic lymphoma, 394
- Anglo-Nubian goats, 460
- Anguina agrostis*, 262
- Angus cattle
cerebellar cortical abiotrophy in, 301, 304
cerebellar malformations in, 85
hypomyelination in, 290
- Aniline blue fixation, 423
- Anisomorphic gliosis, 41-42
- Anisomorphic pineal tumors, 379
- Annulus fibrosus, 199
- Anomaly, spinal cord, 31
- Anophthalmia, 78-79
- Anterograde axonal transport, 403
- Antigen
canine distemper encephalomyelitis, 103
rabies viral, 97, 99
- Antoni schwannoma, 473-474
- Aortic arterial embolism, 453
- Aortic body tumors, 393-394
- Apicomplexa, 162
- Aplasia
caudal vertebral, 87-88
cerebral, 68-69
of corpus callosum, 72
in diencephalon, 78-79
- Apoptosis, 2, 41
- Arabian horse
cerebellar cortical abiotrophy in, 301, 305

Arabian horse—cont'd
 occipitoatlantoaxial malformation in, 198
 spongiform encephalopathies in, 139
 Arachidonic acid metabolites, 38
 Arachnoid, 3
 Arachnoid cysts, 355
 Arachnoid granulations, 3
 Area postrema, 33
 Argininosuccinate synthetase deficiency, 212
 Arhinencephaly, 71-72
 Arnold-Chiari malformation, 79-82
 Arsanilic acid, 252
 Arsenic poisoning, 252-253
 Arterial embolism, 453
 Arthritis
 in encephalitis, 128-129
 in spirochetal infection, 155
 Arthrogryposis
 in hydranencephaly, 73
 in mannosidosis, 460
 Artifacts
 in central nervous system, 32-35, 36
 in peripheral nervous system, 422-423
 ASF; *see* African swine fever
 L-Aspartate, 237
 Aspartylglycosaminuria, 211
Aspergillus
 in encephalomyelitis, 151
 in tremorgenic syndromes, 262
Astragalus
 in mannosidosis, 227-228
 in plant poisoning, 266
 Astroblast, 3
 Astrocytes, 3, 10-18
 Alzheimer type, 12, 210, 211
 in central nervous system injury, 11-18
 classification of, 10
 formation of, 2
 hypertrophic, 13
 in immunological reactions, 11
 products of, 11
 properties of, 11
 roles of, 10-11
 Astrocytoma, 362-370
 in baboon, 369
 in cats, 369
 classification of, 363-364
 in dogs, 364-369
 in mice and rats, 369
 in pigs, 369
 Astrocytosis, 3
 Astroglia
 in gliosis, 42
 tumors of, 362-370; *see also* Astrocytoma
 Astroglisis, 3
 Ataxia
 in calcinosis circumscripta, 205

Ataxia—cont'd
 in cattle, 286-287
 in dogs, 198
 enzootic, 273-277
 in horse, 193
 hound, 321, 322
 in rabbits, 299
 in Terriers, 321-322
 Atherosclerosis
 cerebrovascular, 244
 vascular degeneration in, 53
 Atlantoaxial subluxation, 201
 Atrophy
 cerebellar, 301
 muscular, 308-309, 314
 olivopontocerebellar, 306
 somatofugal, 8-9
 Atypical canine GM₂ gangliosidosis, 461-462
 Aujeszky's disease, 100-102
 Australian cattle dog, 213
 Australian Kelpie, 301, 302
 Australian Merino sheep, 305
 Australian Silky Terrier, 223
 Australian stringhalt, 451
 Autoimmune encephalomyelitis, 17, 18
 Autonomic ganglia, 413-414
 Autonomic nervous system disorders, 469-471
 Autosomal recessive disorders, 215
 Avian; *see* Bird
 Avulsions of brachial plexus, 453-454
 Axolemma, 402
 Axon, 3-5
 aging changes in, 50-51
 degeneration of, 425-426
 Nauta-Gygax technique in, 30
 in ventral spinal roots, 25
 diseases of, 8-9
 in feline hypertrophic neuropathy, 440
 injury to, 190-191
 myelin and, 404
 neuropathy of, 444-445
 peripheral nervous system, 402-404
 transport of, 402-403
 unmyelinated, 406-407
 Axonal reaction, 415-417
 Axonopathy
 in Boxer, 445
 congenital, 31
 in Friesian calves, 325-326
 distal, 8-9, 420-421
 in laryngeal hemiplegia, 448
 in Labrador Retriever, 323-324
 in Rottweiler, 446
 Axonotmesis, 415
 Axoplasm, 402
 Ayrshire cattle
 cerebellar cortical abiotrophy in, 301
 poliomyelomalacia in, 260

B

Babesia, 171
 Baboon
 astrocytomas in, 369
 cerebellar cortical abiotrophy in, 301
Bacillus piliformis, 151
Bacillus thiaminolyticus, 279
 Bacterial infection, 151
 Ballooning, myelin, 406
 Barker foals, 240
 Barr bodies, 412
 Basset Hound
 globoid cell leukodystrophy in, 220
 Lafora body disease in, 327
 vertebral malformation in, 200
 Bat rabies, 97
 Batten disease, 234
Baylisascaris columnaris, 162
Baylisascaris procyonis, 160, 162
 BBB; *see* Blood-brain barrier
 BD; *see* Border disease
 Beagle
 cerebellar cortical abiotrophy in, 301
 gangliosidosis in, 218
 hereditary polyneuropathy in, 441-442
 Lafora body disease in, 327
 lumbosacral stenosis in, 454
 pain syndrome in, 114
 tremorgenic syndromes in, 263
 Bear
 astrocytosis in, 13
 distemper encephalomyelitis in, 102
 senile plaque in, 54
 Beefmaster bull, 236
 Belgian foal, 70
 Bermuda grass, 263
 Bernese Mountain dog
 cerebellar cortical abiotrophy in, 301
 hypomyelination in, 293
 Bernese Running dog, 301
 Beta-cell tumors, 246
 Bielschowsky technique, 29
 Bilirubin encephalopathy, 214
 Biology, molecular, 30-32
 Bird
 brachial plexus avulsion in, 454
 encephalomyelitis in, 124, 145
 pineoblastoma in, 379
 xanthoglioma in, 370
 Birman cat
 leukoencephalomyeloneuropathy in, 452
 spongy degeneration in, 300
 Black and Tan Hound, 424
 Black-tailed deer, 139
Blastomyces dermatitidis, 155
 Blastomycosis, 155
 Blebbing, myelin, 406
 Blindness
 posttraumatic, 204
 in vitamin A deficiency, 271-272

- Blood-brain barrier, 48
 - in hepatic encephalopathy, 211
- Blood vessels
 - aging of, 52-53
 - endoneurial, 409
 - hypertrophy of, 104
- Blue fox, 169-170
- Blue Tick Hound, 424
 - globoid cell leukodystrophy in, 220
- Bluetongue virus, 73
 - cerebellar lesions in, 84
- Bodian technique, 29
- Bone fracture, 190, 191, 192
- Border Collie, 301
- Border disease, 73, 287-290
- Border Leicester lambs, 72
- Borna disease, 148-149
- Borrelia burgdorferi*, 155
- Boston Terrier, 364
- Boutons, 413
- Bouvier des Flanders, 450
- Bovine; *see* Cattle
- Boxer
 - astrocytomas in, 364
 - progressive axonopathy of, 445
- Brachial plexus
 - avulsions of, 453-454
 - neuritis of, 427-428
- Bradykinin, 38
- Brahman cattle, 232
- Brain, 2
 - abscesses of, 156-159
 - epileptic damage to, 244
 - in equine herpesvirus, 146
 - examination of, 27-28
 - in feline infectious peritonitis, 119
 - injuries to, 189-193
 - in listeriosis, 134, 135
 - macrophages of, 22-23
 - malformations of, 68-86
 - in brain stem, 78-82
 - in cerebellum, 82-86
 - in cerebrum, 68-78; *see also* Cerebral malformations
 - metastases in, 392, 393
 - myelin in, 15-16
 - swelling of, 36-39
 - in thrombotic meningoencephalitis, 143
- Brain stem
 - in feline polioencephalomyelitis, 119
 - formation of, 2
 - malformations of, 78-82
- Brittany Spaniel
 - cerebellar cortical abiotrophy in, 301
 - spinal muscular atrophy in, 314
- Bromethalin-based rodenticides poisoning, 267
- Brown Swiss cattle
 - progressive degenerative myoclonic encephalopathy of, 325
- Brown Swiss cattle—*cont'd*
 - spinal muscular atrophy in, 315
- Brucella abortus*, 158
- Bubbling, myelin, 406
- Buckthorn polyneuropathy, 469
- Bull; *see* Cattle
- Bull Mastiff puppy, 299
- Bulldog
 - spinal cord malformations in, 88
 - vertebral malformation in, 200
- Büngner's bands, 4
 - in equine laryngeal hemiplegia, 448, 449
 - in hereditary sensory neuropathy, 442, 443
 - in Wallerian degeneration, 418, 419
- Bunina bodies, 7
- Bunny-hopping gait, 89-90
- Burmese cat
 - craniofacial malformation in, 70
 - encephalocle in, 69
 - optic nerve hypoplasia in, 79
- Buss disease, 141, 144
- Butterfly tumors, 364
- Bystander demyelination, 43
- C**
- C₆ component of complement, 464
- Cache Valley virus, 73
- Cairn Terrier
 - globoid cell leukodystrophy in, 220
 - neuronal abiotrophy of, 306, 307
- Calcinosis circumscripta, 204-205
- Calf; *see also* Cattle
 - Aujeszky's disease in, 102
 - cavitation in, 24
 - cerebellar cortical abiotrophy in, 304
 - cerebral aplasia in, 68-69
 - congenital axonopathy in, 325-326
 - congenital tremor in, 326
 - Dandy-Walker syndrome in, 86
 - encephalomyelopathy in, 326-327
 - ganglioglioma in, 377
 - granulomatous radiculitis in, 436
 - hexachlorophene poisoning in, 258
 - holoencephaly in, 72
 - hydranencephaly in, 72
 - hydrocephalus in, 77
 - hypomyelination in, 290, 299
 - hypovitaminosis A in, 271-272
 - malformations in
 - Arnold-Chiari, 81-82
 - cerebellar, 83-84
 - mannosidosis in, 230
 - Maple syrup urine disease in, 211
 - medullary dysplasia in, 79
 - medulloblastoma in, 378
 - megalencephaly in, 75
 - metabolic disorders in, 212
 - paralysis in
- Calf—*cont'd*
 - paralysis in—*cont'd*
 - facial, 436
 - femoral nerve, 457-458
 - poliomyelomalacia in, 260
 - polymicrogyria in, 74
 - spinal cord duplication in, 86-87
 - spinal cord injury in, 201
 - spinal muscular atrophy in, 315
 - spongy degeneration in, 297-299
- Calvaria, 189-190
- Calving paralysis, 457
- Camel, 277
- Canadian Corriedale lamb, 305
- Canavan's disease, 295
- Cancer; *see* Carcinoma
- Candida*, 151
- Canine; *see* Dog
- Capillary vessels, 23, 24
- Caprine; *see* Goat
- Carbon monoxide poisoning, 267
- Carcinoma
 - choroid plexus, 374, 375
 - ganglioradiculitis and, 430
 - nasal, 391-393
 - prostatic, 393
 - squamous cell, 391
- Carnivores, 280
- Cartilaginous exostosis, 201-202, 391
- Cat
 - adenocarcinoma in, 392
 - ancillary procedures in, 48
 - arterial embolism in, 453
 - astrocytoma in, 369
 - astrocytosis in, 13
 - Aujeszky's disease in, 100-102
 - axonal reaction in, 416
 - brachial plexus avulsion in, 453
 - caudal vertebral aplasia in, 87-88
 - cerebellar cortical abiotrophy in, 301, 304
 - ccrroid-lipofuscinosis in, 234-236
 - congenital shunts in, 208
 - cryptococcosis in, 151-153, 154
 - diabetic neuropathy in, 462
 - dysautonomia in, 470-471
 - encephalocele in, 69
 - encephalomyelitis in
 - immunodeficiency virus, 122
 - parasitic, 159, 162
 - protozoan, 163-165
 - encephalopathy in
 - ischemic, 242-244
 - spongiform, 139
 - ependymoma in, 376
 - facial paralysis in, 447-448
 - gangliosidosis in, 218
 - globoid cell leukodystrophy in, 221, 458
 - glycogenosis in, 232-233

Cat—cont'd

- hydranencephaly in, 73
 - hydrocephalus in, 77
 - hyperchylomicrohememia in, 464
 - hyperlipoproteinemia in, 464
 - hyperoxaluria in, 465
 - hypertrophic polyneuropathy in, 439-440
 - hypomyelination congenita in, 293
 - infectious peritonitis in, 116, 119-121
 - intervertebral disk prolapse in, 204
 - leukoencephalomyeloneuropathy in, 452
 - lipoma in, 355
 - lymphoma in, 393, 394
 - malformations in
 - cerebellar, 82-83
 - craniofacial, 70
 - mannosidosis in, 227, 460
 - medulloblastomas in, 378
 - meningioma in, 361, 362
 - metabolic disorders in, 213
 - microphthalmia in, 79
 - motor neuron disease in, 312
 - mucopolysaccharidosis in, 230-231
 - myelopathy in, 249, 321
 - neuritis in
 - brachial plexus, 427-428
 - demyelinating optic, 122-123
 - neurofibrillary accumulation in, 313
 - neuromyopathy in, 453
 - neuronal aging in, 49-50
 - Niemann-Pick disease in, 224, 460-461
 - oligodendroglioma in, 371
 - optic nerve hypoplasia in, 79
 - panleukopenia virus in, 82-83
 - pituitary tumors in, 383, 384
 - poisoning in
 - hexachlorophene, 258
 - lead, 465
 - mercury, 254
 - thallium, 466
 - polioencephalomyelitis in, 119-122
 - polyceratitis in, 426-427
 - polyradiculoneuritis in, 422, 427
 - rabies in, 99
 - schwannoma in, 476
 - spinal cord injuries in, 191-192
 - spongy degeneration in, 296, 300
 - thiamine deficiency in, 280
- Catarrhal fever, 142-143
- Catecholamines, 153
- Cattle; *see also* Calf
- adenovirus vasculitis in, 118
 - ancillary procedures in, 48
 - ataxia in, 286-287
 - Aujeszky's disease in, 102
 - calving paralysis in, 457
 - cerebellar cortical abiotrophy in, 301, 304
 - cerebellar malformations in, 83-84, 85

Cattle—cont'd

- ceroid-lipofuscinosis in, 234, 236
- citrullinemia in, 212
- congenital axonopathy in, 325-326
- diarrhea virus in, 73, 83-84, 85
- encephalomyelitis in, 144
 - parasitic, 159-161
 - protozoan, 165-167, 171
- encephalomyelopathy in, 325, 326-327
- encephalopathy in
 - hepatic, 209
 - spongiform, 139, 140
- gangliosidosis in, 218
- glycogenosis in, 232
- hepatic encephalopathy in, 209
- herpesvirus meningoencephalomyelitis in, 141
- hydranencephaly in, 73
- hypoglycemia in, 246
- hypomyelination in, 290, 299
- lead poisoning in, 251
- leptomeningitis in, 156, 158
- lipomeningoceles in, 71
- lymphoma in, 394
- malignant catarrhal fever in, 142
- mannosidosis in, 226, 230
- Maple syrup urine disease in, 211
- megalencephaly in, 75
- meningoencephalomyelitis in, 141
- metabolic disorders in, 212
- mycotic encephalitis in, 152, 153
- myeloencephalopathy in, 325
- parainfluenza in, 118
- peripheral nervous system tumors in, 476-481
- pituitary abscess in, 158
- poisoning in
 - cycad, 264
 - lead, 250, 251, 465
 - mercury, 253-254
 - organophosphate, 255
 - plant, 227-228
 - salt, 254-255
 - solanum, 264, 265
- polioencephalomalacia in, 277
- poliomyelomalacia in, 260
- polymicrogyria in, 74
- rabies in, 96, 98
- rhinotracheitis, 141
- rickettsial disease in, 150
- schwannoma in, 480
- spinal muscular atrophy in, 314-315
- spinal myelinopathy in, 325
- spongy degeneration in, 296, 297-299
- thiamine deficiency in, 277-280
- thrombotic meningoencephalitis in, 143-144
- tremorgenic syndromes in, 261-263
- tuberculosis in, 151
- vitamin A deficiency in, 271

- Cauda equina neuritis, 405-406, 432, 433-434
- Cauda equina syndrome, 454-455
- Caudal colliculi hemorrhage, 241
- Caudal vertebral aplasia, 87-88
- Cavanagh's dying back hypothesis, 5
- Cavitation, 24
- Cebocephaly, 72
- Cell ischemia, 239
- Cellular composition of central nervous system, 2-3
- Centaurea*, 263-264
- Central-peripheral distal axonopathy, 421
- Central nervous system, 1-26
 - aging of, 49-55
 - ancillary procedures in, 47-48
 - astrocytes and oligodendrocytes in, 10-18
 - cellular composition of, 2-3
 - cerebral edema in, 36-39
 - choroid plexus epithelium of, 18-19
 - degenerative diseases of, 208-350; *see also* Degenerative diseases
 - embryology and anatomy of, 1-2
 - ependymal cells of, 18-19
 - examination of, 27-36
 - artifacts in, 32-35, 36
 - diseases without lesions in, 35-36
 - fixation in, 29
 - histochemistry and immunohistochemistry in, 29-30, 31
 - molecular biology in, 30-32
 - tissue culture in, 32
 - immunobiology and immunopathology of, 23-25
 - inflammation of, 39-47; *see also* Inflammation
 - inflammatory diseases of, 95-188; *see also* Inflammatory diseases
 - injuries to, 189-207; *see also* Injury
 - macrophages of, 19-23
 - malformations of, 68-94; *see also* Malformation
 - microglial cells of, 19-23
 - microvasculature of, 23, 24
 - neurons in, 4-10
 - neuropathology of, 25-26
 - terms in, 3-4
 - tumors of, 351-401; *see also* Tumors
- Central neurocytoma, 375, 377
- Cerebello-olivary degeneration, 305
- Cerebellum
 - abiotrophy of, 86, 301-305
 - atrophy of, 301
 - formation of, 2
 - hypoplasia of, 25, 26, 301
 - infarction of, 238, 244
 - malformations of, 79, 80, 82-86
 - neuroblastomas of, 375
- Cerebral malformations, 68-78, 79

- Cerebral malformations—cont'd
 agenesis in, 72
 aplasia in, 68-69
 arhinencephaly in, 71-72
 cyclopia in, 71-72
 encephalocle in, 69-71
 exencephaly in, 69-71
 holoencephaly in, 71-72
 hydranencephaly in, 72-73
 hydrocephalus in, 75-77
 hydromyelia in, 77-78
 lissencephaly in, 73-74
 megalencephaly in, 74-75
 meningocele in, 69-71
 meningoencephalocle in, 69-71
 microencephaly in, 74
 pachygyria in, 73-74
 polymicrogyria in, 74
 porencephaly in, 72-73
 syringomyelia in, 77-78
- Cerebrocortical necrosis, 277-280
- Cerebrohepatorenal syndrome, 214
- Cerebrospinal fluid, 3
 in canine distemper encephalomyelitis, 103
- Cerebrovascular accidents, 244
- Cerebrovascular amyloidosis, 54, 55
- Cerebrovascular atherosclerosis, 244
- Cerebrum
 absence of, 68-69
 aplasia of, 68-69
 in canine distemper encephalitis, 104
 edema of, 36-39
 spongy degeneration in, 296-297
 in Swiss Simmental cattle, 298, 299
 formation of, 2
 hypoxia of, 241
 infarction of, 244
 ischemia of, 237
 malformations of; *see* Cerebral malformations
 necrosis of, 242, 244-246
 neuroblastomas of, 375
 oligodendrocyte in, 14
- Ceroid, 50, 52
- Ceroid-lipofuscinosis, 233-236
- Cervical stenotic myelopathy, 193-198
- Cervical vertebral malformation-malarticulation, 198-199, 200, 201
- Charolais cattle
 cerebellar cortical abiotrophy in, 301
 progressive ataxia of, 286-287
- Chastek paralysis, 280
- Chicken
 enterovirus encephalomyelitis, 124
 glioma in, 369-370
 Newcastle disease in, 118
 poliomyelomalacia in, 260
 riboflavin deficiency in, 463-464
 vitamin E deficiency in, 272
- Chihuahua
 atlantoaxial subluxation in, 201
 hypoglycemia in, 246
 neuroaxonal dystrophy in, 316
- Chlorinated hydrocarbon insecticide poisoning, 256-257
- Cholera, hog, 84, 125-126
- Cholesterol granuloma, 52
- Chondrodystrophic breed of dogs, 202
- Chondroid chordoma, 386
- Chordomas, 386, 387
- Choroid plexus, 3
 aging of, 52-53
 epithelium of, 18-19
 in feline infectious peritonitis, 119
 papilloma of, 352
 tumors of, 373-375
- Chow dog
 cerebellar cortical abiotrophy in, 301
 hypomyelination in, 292
- CHP; *see* Coonhound paralysis
- Chromatolysis, 3, 5-7
 central, 415-417
- Chromophobe tumors, 382-384
- Chronic wasting disease, 139
- Chuzan virus, 73
- Ciliary neurotrophic factor, 403, 418
- Circulatory disorders, 208-249; *see also* Metabolic disorders
- Citrullinemia, 212
- Cladosporium bantianum*, 155
- Clavibacter*, 262
- Claviceps*, 262-263
- Clostridium perfringens*, 269-270
- Clostridium sporogenes*, 279
- CNN; *see* Cerebrocortical necrosis
- CNTF; *see* Ciliary neurotrophic factor
- Coccidioides immitis*, 155
- Cockatiel, 379
- Cocker Spaniel, 307
- Coenurus cerebralis*, 161
- Collagen pockets, 407
 in equine laryngeal hemiplegia, 448, 449
 myelinated axon degeneration and, 420
- Collie
 cerebellar cortical abiotrophy in, 301
 neuroaxonal dystrophy in, 316
- Colloid cysts, 354
- Complement
 deficiency of, 464
 in meningeal polyarthritis, 116
- Compression
 peripheral nerve, 242
 spinal cord, 192, 195-198
 in Wallerian degeneration, 25
- Concussion, 190
- Congenital axonopathy, 31
 in Friesian calves, 325-326
- Congenital cerebral edema, 296-297
- Congenital hydrocephalus, 77
- Congenital hypomyelinating polyneuropathy, 441
- Congenital hypomyelination, 298
- Congenital myoclonus, 297
- Congenital tetany, 298
- Congenital tremor, 290-292, 326
- Contact phenomena, 190
- Contrecoup contusions, 190
- Contusion, 190-191
- Convulsive foal syndrome, 240
- Coonhound paralysis, 424, 426
- Copper
 deficiency of, 273-277
 chromatolytic neurons in, 5
 poisoning with, 211
- Cordy's disseminated encephalomyelitis, 110
- Coronavirus encephalomyelitis, 149
- Corpus callosum, agenesis of, 72
- Corpuscles, granular, 21, 22
- Corriedale sheep
 cerebellar cortical abiotrophy in, 301, 305
 glycogenosis in, 233
- Cortical abiotrophy, cerebellar, 86
- Cortical hypoplasia, cerebellar, 25, 26
- Cortical necrosis, laminar, 104
- Corticospinal projections, 25, 26
- Corticosteroids, 156
- Corynebacterium pseudotuberculosis*, 158
- Corynebacterium rathayi*, 262
- Corynebacterium tenuis*, 265-266
- Corynetoxins, 262
- Coup contusions, 190
- Cow; *see* Calf; Cattle
- Cowdria ruminantium*, 150
- Coyote
 adenovirus-induced vasculitis in, 117
 distemper encephalomyelitis in, 102
- Coyotillo polyneuropathy, 469
- Cranial nerve
 second
 degeneration of, 204
 glioblastoma of, 367
 hypoplasia of, 78-79
 infarction of, 249
 fifth, 475
 seventh, 436
 eighth, 436
- Cranial neuritis, 436-437
- Craniofacial malformations, 70
- Craniopharyngioma, 385, 386
- Craniothoracopagus, 71
- Cranium bifidum, 69
- Creutzfeldt-Jakob disease, 139-141
- Crush artifact, 422
- Cryptococcus neoformans*, 151-153
- Crystalline inclusions, 405-406
- CSF; *see* Cerebrospinal fluid

- Cuffing, 429, 430
Culex, 145
Culiseta, 145
 Culture, tissue, 32
 Curled toe paralysis, 463-464
Cuterebra, 162, 163
Cuterebra larva, 243-244
 CVMM; *see* Cervical vertebral malformation-malarticulation
 Cyanide poisoning, 267
 Cycad poisoning, 264-265
 Cyclopia, 71-72
 Cynomolgus monkey, 236
 Cyst, 352-355
 Coenurus, 161
 epidural synovial, 198
 formation of, 24
 Cysticercosis, 161
Cysticercus cellulosae, 161
 Cytoplasm, 4
 Cytoplasmic bodies
 in gangliosidosis, 219, 220
 in rabies, 97, 98
 Cytoplasmic inclusions, 7
 in canine distemper encephalitis, 104
 in rabies, 96, 98
 Cytoplasmic vacuoles, 7
 Cytotoxic edema, 38-39
- D**
- Dachshund
 ceroid-lipofuscinosis in, 234
 intervertebral disk disease in, 202
 sensory neuropathy in, 443-444
 Daft lamb disease, 305
 Dalmatian
 cerebral malformation in, 78
 hypomyelination in, 293
 laryngeal paralysis in, 451
 leukodystrophy in, 282
 Dancing Doberman disease, 447
 Dancing pig disease, 290-291
 Dandelion stringhalt, 451
 Dandy-Walker syndrome, 86
 cerebellar malformations in, 85
 cerebral malformations in, 79
 Danish calves, 315
 Dark neurons, 35
 Deafness, 50
 Decarboxylase deficiency, branched-chain
 ketoacid, 297-298
 Deer
 ancillary procedures in, 48
 cerebral abscess in, 158
 chronic wasting disease in, 139
 copper deficiency in, 276-277
 epiphyseal fracture in, 191
 hypoglycemia in, 246
 malignant catarrhal fever in, 142
 parasitic encephalomyelitis in, 159-161
 Deer—cont'd
 polioencephalomalacia in, 277
 tremorgenic syndrome in, 261-263
 Degeneration
 atherosclerotic vascular, 53
 of axons, 25, 30
 granulovacuolar, 54
 in gray matter, 299-300
 hereditary porcine neuronal system, 306
 Holmes cerebello-olivary, 305
 of neurons, 4-5
 optic nerve, 204
 in spinal cord injury, 195, 196-198
 spongy, 282, 295-300
 Wallerian; *see* Wallerian degeneration
 in white matter, 282
 Degenerative diseases
 of central nervous system, 208-350
 hereditary familial and idiopathic,
 281-327; *see also* Hereditary and
 idiopathic degenerative diseases
 intoxications and toxicoinfectious dis-
 eases in, 250-271; *see also* Poison-
 ing
 metabolic and circulatory disorders
 in, 208-249
 metabolic disorders in; *see also* Meta-
 bolic disorders
 nutritional, 271-280; *see also* Nutri-
 tional disorders
 of peripheral nervous system, 437-453
 congenital hypomyelinating polyneu-
 ropathy in, 441
 dancing Doberman disease in, 447
 distal denervating disease in, 447
 epizootic peroneal and tibial neuropa-
 thy in, 446
 focal trigeminal hypertrophic neurop-
 athy in, 440
 giant axonal neuropathy in, 444-445
 hereditary polynuropathy in, 441-442
 hereditary sensory neuropathy in,
 442-443
 hypertrophic neuropathy in, 437-439
 hypertrophic polyneuropathy in, 439-
 440
 idiopathic facial paralysis in, 447-448
 ischemic neuromyopathy in, 453
 kangaroo gait in, 452-453
 laryngeal paralysis in, 448-451
 leukoencephalomyeloneuropathy in,
 452
 neuropathy in, 446-447
 polyneuropathy in, 445-446
 progressive axonopathy in, 445
 sensory neuropathy in, 443-444
 stringhalt in, 451-452
 Degenerative myelocnecephalopathy, 317-
 319
 paresis and ataxia in, 193
 Degenerative myeloencephalop-
 athy—cont'd
 progressive, 325
 vitamin E deficiency in, 273
 Degenerative myelopathy, 319-321
 Delayed organophosphate poisoning, 255-
 256
 Demyelination, 16, 25, 42-44
 in idiopathic polyradiculoneuritis, 425
 in intervertebral disk disease, 203
 in optic neuritis, 122-123
 segmental, 421-422
 Dendrites, 4, 5
 Dendritic microglia, 21
 Denervating disease, 447
Dermacentor, 150-151
 Dermoid cysts, 355
 Devon cattle, 234, 236
 Diabetic neuropathy, 462
 Diarrhea, bovine virus, 73, 83-84, 85
 Diastematomyelia, 86-88
 Dichlorophen, 267
 Diencephalon, 2
 malformations in, 78-79
 Diffuse axonal injury, 190-191
 Digestion chambers, 417
 Digital neuroma, 456
 Diphtheria toxin, 421
Diplodia maydis, 468-469
 in tremorgenic syndromes, 262
 Diplomyelia, 86-88
Dirofilaria immitis
 in cerebrovascular accidents, 244
 levamisole in, 258
 in parasitic encephalomyelitis, 159, 162
 Disk disease, intervertebral, 202-204
 Disseminated encephalomyelitis, 110
 Distal axonopathy, 8-9
 laryngeal hemiplegia in, 448
 in peripheral nervous system, 420-421
 Distal denervating disease, 447
 Distemper encephalomyelitis, 102-110, 163
 diagnosis of, 103
 etiology of, 102-103
 in gray matter disease, 103-105
 pathogenesis of, 106-110
 signs of, 103
 in white matter disease, 105-106
 Distemper virus-infected glial cells, 31
 Distraction, 192
 Doberman Pinscher
 cervical vertebral malformation-malarti-
 culation in, 198
 fibrocartilaginous embolic myelopathy
 in, 248
 germ cell tumors in, 385
 motor neuron degeneration in, 309
 progressive neuromuscular disorder in,
 447
 thoracic hemivertebra in, 200

Dog

adenovirus vasculitis in, 117, 118
 aging changes in, 51
 ancillary procedures in, 48
 anesthesia-related syndromes in, 241
 ascending myelomalacia in, 204
Aspergillus terreus infection in, 151
 astrocytoma in, 364-369
 ataxia in, 321-322
 atlantoaxial subluxation in, 201
 Aujeszky's disease in, 100, 101
 axonal reaction in, 415
 axonopathy in, 323-324
 blastomycosis in, 155
 brachial plexus avulsion in, 453
 brachial plexus neuritis in, 427-428
 calcinosis circumscripta in, 204
 cauda equina syndrome in, 454-455
 cerebellar cortical abiotrophy in, 301, 302-304, 305
 cerebellar infarction in, 238, 244
 cerebrovascular amyloid in, 54
 ceroid-lipofuscinosis in, 234
 chromatolysis in, 6
 congenital shunts in, 208
 corpus callosum aplasia in, 72
 craniopharyngioma in, 385
 cryptococcosis in, 151-153, 154
 cysts in
 arachnoid, 355
 epidermoid, 354-355
 formation of, 24
 Dandy-Walker syndrome in, 86
 demyelinating disease in
 of central nervous system, 284-285
 of peripheral nervous system, 422
 dirofilariasis in, 258
 distemper virus-infected glial cells, 31
 dysautonomia in, 470, 471
 ehrlichiosis in, 151
 encephalitis in, 110, 111-114, 115
 encephalitozoonosis in, 169
 encephalomyelitis in
 distemper, 102-110; *see also* Distemper encephalomyelitis
 herpesvirus, 117
 parasitic, 162
 protozoan, 163-165
 endoplasmic reticulum of, 411
 ependymoma in, 376
 frontal bone fracture in, 190
 fucosidosis in, 224, 226, 459-460
 gangliocytoma in, 375
 ganglionitis in, 431
 ganglioradiculitis in, 428-431
 gangliosidosis in, 217, 218
 with muscle weakness and wasting, 461-462
 glioblastoma in, 365
 glioma in, 364

Dog—cont'd

gliomatosis in, 380
 glycogenosis in, 232, 233
 herpesvirus in, 84-85
 hydrocephalus in, 76, 77, 78
 hydromyelia in, 77-78
 hypoglycemia in, 246
 hypomyelination in, 292, 293
 hypomyelinogenesis in, 291-293
 hypothyroidism in, 462-463
 insulinoma in, 472-473
 intervertebral disk disease in, 202
 Lafora body disease in, 327
 leptomenigitis in, 156
 leukodystrophy in, 282-286
 globoid cell, 220-222, 458
 leukoencephalomyelopathy of, 285
 leukomyelopathy in, 319-321
 lissencephaly in, 74
 lumbosacral stenosis in, 454
 malformations in
 cerebellar, 84-86
 cerebral, 78
 spinal cord, 88, 89
 vertebral, 198, 200
 medulloblastoma in, 378
 meningeal polyarteritis in, 114
 meningioangiomas in, 353-354
 meningioma in, 355-361
 meningoencephalomyelitis in, 118-119
 granulomatous, 110-111, 112
 metabolic disorders in, 212, 213
 microgliomatosis in, 380, 381
 motor neuron disease in, 308-309
 mucopolysaccharidosis in, 230-231
 myelin in, 406
 myelinated axon in, 404
 myelopathy in, 321, 324
 fibrocartilaginous embolic, 246-249
 nervous system degeneration in, 322-323
 neuroaxonal dystrophy in, 315-316
 neurofibrillary accumulation in, 313
 neurogenic muscular atrophy in, 308-309
 neuromuscular disorder in, 447
 neuronal abiotrophy in, 306-307
 neuronal aging in, 49-50
 neuropathy in, 446-447
 diabetic, 462
 epizootic peroneal and tibial, 446
 giant axonal, 444-445
 hereditary sensory, 442-443
 inherited hypertrophic, 437-439
 paraneoplastic, 472
 sensory, 443-444
 Niemann-Pick disease in, 224, 225
 oligodendroglioma in, 370-373
 onion bulb formations in, 422
 optic nerve glioblastoma in, 367

Dog—cont'd

optic nerve hypoplasia in, 79
 pain syndrome in, 114
 parainfluenza virus in, 117
 paralysis in
 idiopathic facial, 447-448
 laryngeal, 450-451
 Stockard's, 308
 perineurium of, 408
 peripheral nerves in, 407
 poisoning in
 ethylene glycol, 257
 hexachlorophene, 258
 lead, 465
 mercury, 254
 pyridoxine, 467-468
 salmon, 151
 thallium, 466
 polyarthritis in, 116
 polymicrogyria in, 74
 polyneuropathy in, 445-446, 473
 congenital hypomyelinating, 441
 hereditary, 441-442
 idiopathic, 426
 polyradiculoneuritis in, 422, 424-427
 protothecosis in, 156
 protozoan radiculoneuritis in, 434-436
 rabies in, 96-99
 Renaut bodies of, 409
 reticulosis in, 379
 Rocky Mountain spotted fever in, 151
 schwannoma in, 478
 seizure disorders in, 245-246
 senile plaque in, 54, 55
 spinal cord compression in, 196, 197, 200
 spinal cord injuries in, 191-192, 198-201
 spinal ganglia of, 411
 spinal muscular atrophy in, 309, 314
 spongy degeneration in, 295-296, 299-300
 sympathetic neurons of, 413, 414
 syringomyelia in, 77-78
 thiamine deficiency in, 280
 thoracic hemivertebra in, 200
 toxoplasmosis in, 434-436
 tremorgenic syndromes in, 262, 263
 tumors in
 aortic body, 393-394
 choroid plexus, 352, 373-375
 germ cell, 385
 malignant peripheral nerve sheath, 476, 477, 478
 metastatic brain, 392
 peripheral nervous system, 474-476, 477, 478
 pituitary, 380-384
 spinal cord, 386-391
 vascular hamartoma in, 353

Dog—cont'd
 white matter degeneration in, 50, 51
 Dolphin, 102
 Dopamine deficiency, 264
 Dorsal lamina, vertebral, 199
 Dorsal root radiculitis, 25, 26
 Dorset sheep, 221
 Downer cows, 457
 Doxorubicin, 457
 Dumb rabies, 96
 Dummy foals, 240
 Dura mater, 3
 Duret hemorrhage, 37, 191
 Dying back hypothesis of Cavanagh, 5
 Dying back neuropathies, 420-421
 Dynamic megalencephaly, 74
 Dynamic stenosis, 195
 Dynamin, 403
 Dysautonomia, 469-471
 chromatolytic neurons in, 5
 Dysmyelinating diseases, 281
 Dysplasia
 medullary, 79
 oligodendroglial, 287
 Dystrophy
 inherited neuronal, 464
 neuroaxonal, 8-9, 315-317
 term, 281

E

EAE; *see* Experimental autoimmune encephalomyelitis
 EAN; *see* Experimental allergic neuritis
 Eastern encephalomyelitis, 144
 Edema, 267-269
 axonal, 8
 brain, 36-39
 cerebral, 36-39
 spongy degeneration in, 296-297
 in Swiss Simmental cattle, 298, 299
 cytotoxic, 38-39
 in gangliosidosis, 218
 neuraxial, 297
 pulmonary, 37
 spheroids in, 8
 vasogenic, 38, 39
 EE; *see* Eastern encephalomyelitis
 Egyptian Mau cat, 296
 Ehrlichiosis, 151
 Eighth cranial nerve, 436
 Eland, 139
Elaphostrongylus rangiferi, 161
 Electron microscopy, 29
 Elk, 139
 Elzholz bodies, 405
 Embolic myelopathy, 246-249
 Embolism, arterial, 453
 Embryology, 1-2
 EMC virus; *see* Encephalomyocarditis virus

Empyema, 436-437
 Encephalitis
 arthritis, 128-129
 in Aujeszky's disease, 101
 Japanese, 146
 Murray Valley, 146
 mycotic, 152, 153
 old dog, 110
 Pug dog, 111-114, 115
 pyogranulomatous, 155
 in rabies, 97
Encephalitozoon, 169-170
 Encephalocele, 69-71
 Encephalomalacia
 after intracarotid injection, 246
 focal symmetrical, 269-270
 nigropallidal, 263-264
 Encephalomyelitis
 autoimmune, experimental, 17, 18
 avian, 124, 145
 canine distemper, 102-110, 163; *see*
 also Distemper encephalomyelitis
 canine herpesvirus, 117
 disseminated, 110
 enterovirus, 123-125
 equine viral, 144-146
 feline immunodeficiency virus, 122
 fungal agents in, 151
 hemagglutinating, 126-127
 murine coronavirus, 149
 Newcastle disease, 117-118
 Ontario, 127
 parainfluenza, 117-118
 parasitic, 159-162, 163
 porcine, 125-128
 protozoan, 162-171; *see also* Protozoan
 encephalomyelitis
 rabies virus in, 95
 sporadic bovine, 144
 Venezuelan, 144
 verminous, 159, 160
 viral, 144-146
 Encephalomyelopathy
 equine herpesvirus 1, 146, 147
 necrotizing, 212
 in Simmental and Limousin calves, 326-327
 Encephalomyocarditis virus, 128
 Encephalopathy
 bilirubin, 214
 hepatic, 208-211
 ischemic, 242-244
 renal, 208-211
 spongiform, 139-141, 299
 thiamine deficiency, 277-280
 transmissible, 139-141
 uremic, 211
 Wernicke's, 277
 Encrustation, neuronal, 7
 Endodermal cysts, 354

Endoneurium, 408-409
 fibrosis of, 448, 449
 Endoplasmic reticulum
 in dog, 411
 rough, 415
 smooth, 403-404
 Energy-deprivation change, 239
 English Bulldog
 spinal cord malformations in, 88
 vertebral malformation in, 200
 English Pointer, 308
 English Springer Spaniel
 fucosidosis in, 224
 gangliosidosis in, 218
 glycogenosis in, 233
Entamoeba, 170
 Enteric ganglionitis, 431
 Enterotoxemia, 269
 Enterovirus encephalomyelitis, 123-125
 Entrapment, nerve, 458
 Enzootic ataxia, 273-277
 Enzootic paresis, 123
 Eosin fixation, 423
 Ependymal cells, 3, 18-19
 Ependymal cysts, 354
 Ependymal tumors, 375, 376
 Epicardial plexus tumor, 476, 478
 Epidemic tremor, 124
 Epidermoid cysts, 354-355
 Epidural hematoma, 191
 Epidural synovial cysts, 198
 Epileptic brain damage, 244
 Epineurium, 407
 Epiphyseal fracture, 191
 Epithelium, choroid plexus, 18-19
 Epizootic peroneal and tibial neuropathy, 446
 Epstein-Barr virus, 143
 Equine; *see* Horse
Equus burchelli, 317
Equus przewalskii, 317
Escherichia coli, 268
 Ethylene glycol poisoning, 257-258
Eupatorium rugosum, 263
 Ewes, 452-453
 Excitatory neurotransmitters, 237-238
 Excitotoxin-mediated neuronal injury, 237-238
 Exencephaly, 69-71
 Exostosis, multiple cartilaginous, 201-202, 391
 External germinal cells, 32
 Extrahepatic shunts, 208
 Extravasation, leukocyte, 40

F

Face, monkey, 72
 Facial nerve radiculitis, 436
 Facial paralysis, 447-448
 Falx meningioma, 356, 357

- Farmed deer
 malignant catarrhal fever in, 142
 tremorgenic syndrome in, 261-263
- Fascicles, 407
- Fat granule cells, 21, 22
- Fatty acids, 211
- FCEM; *see* Fibrocartilaginous embolic myelopathy
- Feline; *see* Cat
- Femoral nerve paralysis, 457-458
- Fern, Jimmy, 263
- Ferret
 chordoma in, 387
 distemper encephalomyelitis in, 102
- Fever
 malignant catarrhal, 142-143
 Rocky Mountain spotted, 150-151
 swine, 125-126
- Fibers of Remak, 420
- Fibrillary astrocytomas, 363
- Fibrinoid leukodystrophy, 281, 282
- Fibroblastic meningioma, 358, 360
- Fibroblasts, endoneurial, 408, 409
- Fibrocartilaginous embolic myelopathy, 246-249
- Fibrosis
 endoneurial, 448, 449
 in old animals, 52
- Fifth cranial nerve tumor, 475
- Finnish Harrier, 301
- Finnish Landrace lamb, 116
- Fish, 480
- Fixation
 artifacts and, 422-423
 for electron microscopy, 29
- Flood plain staggers, 262
- Foal; *see also* Horse
 astrocytosis in, 13
 cerebellar cortical abiotrophy in, 305
 craniofacial malformation in, 70
 Dandy-Walker syndrome in, 86
 hydrocephalus in, 77
 neonatal maladjustment syndrome in, 240-241
 optic nerve hypoplasia in, 79
 spinal cord hamartoma in, 90
- Focal meningeal hemorrhage, 191
- Focal symmetrical encephalomalacia, 269-270
- Focal symmetrical poliomyelomalacia, 258-261
- Focal trigeminal hypertrophic neuropathy, 440
- Fontana, spiral bands of, 407, 423
- Foramen, 199
- Forebrain, 2
- Formalin fixation, 423
- Fowl; *see* Chicken
- Fox
 adenovirus-induced vasculitis in, 117
- Fox—cont'd
 distemper encephalomyelitis in, 102
 encephalitozoonosis in, 169-170
 rabies in, 96, 99-100
 salmon poisoning in, 151
 spongy degeneration in, 296
 thiamine deficiency in, 280
- Fox Terrier
 cerebellar cortical abiotrophy in, 301
 cerebellar malformations in, 85
 lissencephaly in, 74
 myelopathy in, 321
- Fractures, 190, 191, 192
- French Bulldog, 200
- Friesian cattle
 congenital axonopathy in, 325-326
 gangliosidosis in, 218
 metabolic disorders in, 212
- Frontal bone fracture, 190
- FSE; *see* Focal symmetrical encephalomalacia
- Fucosidosis
 central nervous system and, 224-226
 peripheral nervous system and, 459-460
- Fungus
 infection with, 151-155
 in tremorgenic syndromes, 261
- Furazolidone poisoning, 267
- Fusarium moniliforme*, 270
- Fusarium tricinctum*, 271
- G
- Gait
 bunny-hopping, 89-90
 in cerebellar disorders, 305
 kangaroo, 452-453
- Galactosemia, 212
- Galactosialidosis, 230
- β -Galactosidase, 218
- Galactosylceramidase 1, 220
- Galloway cattle, 226
- Ganglia
 autonomic, 413-414
 sensory, 410
 spinal, 410-411, 412
- Gangliocytoma, 375
- Ganglioglioma, 375, 377, 378
- Ganglioneuroblastoma, 375
- Ganglionitis
 in Aujeszky's disease, 101, 102
 enteric and myenteric, 431
 in rabies, 95, 97
 in swine, 125
- Ganglioradiculitis, 428-431
- Gangliosidosis, 216, 217, 218-220
 with muscle weakness and wasting, 461-462
- GAP; *see* Growth-associated phosphoprotein
- Gaucher's disease, 221-223
- GBS; *see* Guillain-Barré syndrome
- GCL; *see* Globoid cell leukodystrophy
- Gemistocytic astrocytoma, 363, 368, 369
- Gembok, 139
- Genetics in lysosomal storage diseases, 214-216
- Genistocytes, 12
- Gerbil, 151
- Germ cell tumor, 384-385
- German Shepherd
 Aspergillus terreus infection in, 151
 calcinosis circumscripta in, 204
 cauda equina syndrome in, 454-455
 chronic progressive leukomyelopathy in, 319-321
 giant axonal neuropathy in, 444-445
 glycogenosis in, 232
 neuropathy in, 446-447
 spinal cord tumors in, 386
 spinal muscular atrophy in, 309
- German Shorthair Pointer
 gangliosidosis in, 218
 thoracic hemivertebra in, 200
- Germinal cells, 32-33
- Germinoma, 385
- Gerstmann-Sträussler syndrome, 141
- GFAP; *see* Glial fibrillary acidic protein
- Giant axonal neuropathy, 444-445
- Gid, 161
- Glanders, 151
- Glasser's disease, 156
- Glees technique, 29
- Glia limitans, 11
- Glial cell, 2-3
 aging of, 49-50
 in canine distemper encephalitis, 104
 distemper virus-infected, 31
 in inflammatory response, 42
- Glial fibrillary acidic protein, 10
- Glial shrunken, 3
- Glioblastoma, 364, 365, 366
 optic nerve, 367
- Glioblastoma multiforme, 363-364
- Glioma
 canine, 364
 fowl, 369-370
- Gliomatosis cerebri, 364, 380
- Gliosarcoma, 364
- Gliososis, 3
 aging and, 50
 in Aujeszky's disease, 101
 inflammation and, 39-42
 in scrapie, 137
- Glitter cells, 21, 22
- Globoid cell leukodystrophy
 in Cairn Terrier, 306
 central nervous system and, 220-221, 222, 223
 peripheral nervous system and, 458-459

- Glomerulonephritis, mesangiocapillary, 116
- α -1,4-Glucan 6-glucosyltransferase, 233
- Glucocerebrosidase, 221-223
- Glucosidase, 231
- Glutamate, 38, 237
- Glutaraldehyde fixation, 29, 423
- Glycogenosis, 231-233
- Glycol poisoning, 257-258
- Glycoprotein, 15, 405
- Glycoproteinoses, 224-230
- neuronal, 52, 327
- Glycosaminoglycans, 230-231
- GM₂ gangliosidosis, 461-462
- Goat
- ancillary procedures in, 48
- arthritis encephalitis in, 128-129, 130
- ceroid-lipofuscinosis in, 234, 236
- copper deficiency in, 276
- delayed swayback in, 275
- enterotoxemia in, 270
- hemivertebra in, 201
- hypoglycemia in, 246
- insecticide poisoning in, 256
- mannosidosis in, 228-230, 460
- motor neuron disease in, 312
- mucopolysaccharidosis in, 230-231
- parasitic encephalomyelitis in, 159-161
- polioencephalomalacia in, 277
- poliomyelomalacia in, 24, 260
- polyradiculoneuritis in, 427
- ricketsial disease in, 150
- Sanfilippo disease in, 231
- scrapie in, 136, 139
- spinal cord of, 4
- thiamine deficiency in, 277-280
- toxoplasmosis in, 165
- viral leukoencephalomyelitis of, 128
- Golden Retriever
- cerebellar cortical abiotrophy in, 301
- congenital hypomyelinating polyneuropathy in, 441
- polymicrogyria in, 74
- Golgi network
- incrustation of, 240
- in sensory perikarya, 411-412
- Golgi stain, 29
- Gomori methenamine silver, 30
- Goose
- globoid cell leukodystrophy in, 221
- riboflavin deficiency in, 463-464
- Gordon Setter, 301, 304
- Gotland pony, 301, 305
- Gram stains, 30
- Granular cell tumors, 362, 364
- Granular corpuscles, 21, 22
- Granulations, arachnoid, 3
- Granule cells
- fat, 21, 22
- neurons of, 34
- Granule cells—cont'd
- Reich, 405
- Granuloma, cholesterol, 52
- Granulomatous meningoencephalomyelitis, 110-111, 112, 113
- Granulomatous radiculitis, 436
- Granulovacuolar degeneration, 54
- Grass, 261-263
- Grass sickness, 414, 469-471
- Gray matter
- in canine distemper encephalomyelitis, 103-105
- formation of, 2
- microglia in, 20
- oligodendrocytes in, 12
- in Pug dog encephalitis, 114
- spongy degeneration in, 299-300
- Great Dane
- cerebellar cortical abiotrophy in, 301
- cervical vertebral malformation-malarticulation in, 198
- motor neuron disease in, 308
- Great Dane-Bloodhound crosses, 308
- Greater Kudu, 139
- Greyhound, 301
- Griseofulvin, 69
- Growth-associated phosphoprotein, 418
- Growth factor
- nerve, 403, 418
- platelet-derived, 10
- Guillain-Barré syndrome, 426
- Guinea pig, 169
- Guttural pouch mycosis, 436-437
- Gyri, 2
- H**
- Haemophilus agni*, 156
- Haemophilus somnus*, 143, 144
- Haemophilus suis*, 156
- Haffinger horse, 317
- Hairy shakers, 288
- Halicephalobus deletrix*, 162
- Hamartoma, 352-355
- spinal cord, 90
- Hammondia*, 162
- Hamster, 294-295
- Hawaiian goose, 221
- Hawk, 454
- HC; see Hog cholera
- HE; see Hepatic encephalopathy
- Head trauma, 190
- Heartwater, 150
- Helichrysum argyrosphaerum*, 266
- Hemagglutinating encephalomyelitis virus, 126-127
- Hemangioma, 354
- Hemangiomas, 354
- Hemangiopericytoma, 359
- Hemangiosarcoma, 392, 393
- Hematoma, 191
- Hemiplegia, laryngeal, 448-450
- Hemivertebrae, 200
- Hemorrhage
- in brain swelling, 37
- in caudal colliculi, 241
- duret, 37, 191
- in infarction, 244
- in internal capsule, 26
- meningeal, 191
- in myelopathy, 241-242
- subarachnoid, 191
- Heparin fixation, 29
- Hepatic encephalopathy, 208-211
- Hepatic steatosis, 246
- Hereditary and idiopathic degenerative diseases, 281-327
- ataxia in, 299, 321-322
- axonopathy in, 323-326
- encephalomyelopathy in, 326-327
- hypomyelinogenesis in, 287-295
- in Ibizan Hound, 322-323
- leukodystrophies in, 282-287
- motor neuron diseases in, 307-315
- myeloencephalopathy in, 317-319
- myelopathy in, 319-321, 324-325
- neuraxial edema in, 297
- neuroaxonal dystrophy in, 315-317
- neuronal abiotrophy in, 300-307
- neuronal glycoproteinoses in, 327
- neuronal system degeneration in, 306
- progressive myelinopathy in, 325
- progressive myeloencephalopathy in, 325
- spinal muscular atrophy, 314
- spongy degeneration in, 295-300
- Hereditary polyneuropathy, 441-442
- Hereditary sensory neuropathy, 442-443
- Hereford cattle
- cerebellar cortical abiotrophy in, 301, 304
- cerebellar malformations in, 85
- hypomyelinogenesis in, 290
- Maple syrup urine disease in, 211
- polymicrogyria in, 74
- spinal muscular atrophy in, 314-315
- spongy degeneration in, 297-299
- Herpesvirus, 84-85
- Herpesvirus encephalomyelitis, 117
- Herpesvirus 1 encephalomyelopathy, 146, 147
- Herpesvirus meningoencephalomyelitis, 141
- Herpesvirus suis*, 100
- HEV; see Hemagglutinating encephalomyelitis virus
- Hexachlorophene poisoning, 258
- β -Hexosaminidase, 218
- Hindbrain, 2
- Hippocampus
- formation of, 2

- Hippocampus—cont'd
in transmissible mink encephalopathy, 140
- Hirano bodies, 7
- Histamine, 38
- Histochemistry, 29-30, 31
- Histophilus ovis*, 144
- Histoplasmosis, 155
- Hog; *see* Pig
- Hog cholera vaccine virus, 84
- Holmes cerebello-olivary degeneration, 305
- Holmes stains, 29
- Holoencephaly, 71-72
- Holstein cattle
cerebellar cortical abiotrophy in, 301
congenital axonopathy in, 325-326
lipomeningoceles in, 71
- Homocystinuria, 211
- Hormone, adrenocorticotrophic, 382
- Horse
amputation neuroma in, 455
ancillary procedures in, 48
astrocytosis in, 13
Aujeszky's disease in, 100
autonomic ganglia of, 414
Borna disease in, 148
brain abscesses in, 158
cauda equina neuritis in, 432, 433
cerebellar cortical abiotrophy in, 301, 305
cerebral necrosis in, 242
ceroid-lipofuscinosis in, 236
cranial neuritis in, 436-437
cryptococcosis in, 151-153
crystalline inclusions in, 405-406
Dandy-Walker syndrome in, 86
degenerative myeloencephalopathy in, 317-319
paresis and, 193
vitamin E deficiency and, 273
dysautonomia in, 469, 470
encephalomalacia in, 246
encephalomyelitis in
parasitic, 159, 161-162
protozoan, 167-169
viral, 144-146
epidermoid cyst in, 355
femoral nerve paralysis in, 457-458
focal trigeminal hypertrophic neuropathy in, 440
ganglionitis in, 431
glanders in, 151
granulomatous meningoencephalitis in, 113
grass sickness in, 469-470
herpesvirus 1 encephalomyelopathy in, 146, 147
hydrocephalus in, 77
- Horse—cont'd
infectious anemia in, 146-148
immune complex formation in, 116
intervertebral disk prolapse in, 204
laryngeal hemiplegia in, 448-450
leukoencephalomalacia in, 270-271
lymphoma in, 394
malformations in
cerebellar, 85
occipitoatlantoaxial, 198
meningoencephalocle in, 70
motor neuron disease in, 309-311
myelin in, 406
myelopathy in
fibrocartilaginous embolic, 247, 249
postanesthetic hemorrhagic, 241-242
myopathy in, 242
neonatal maladjustment syndrome in, 240-241
nerve entrapment in, 458
neuroaxonal dystrophy in, 317
nigropallidal encephalomalacia in, 263-264
optic nerve degeneration in, 204
optic nerve hypoplasia in, 79
pituitary tumors in, 384
poisoning in
lead, 251, 465
mercury, 467
plant, 227-228, 266
rabies in, 96
Renaut bodies of, 409
schwann cells in, 407
spinal cord hamartoma in, 90
spinal cord injury in, 193-198
spinal ganglia of, 412
spongiform encephalopathy in, 139
sympathetic ganglia of, 414
tremorgenic syndrome in, 261-263
Trypanosoma infection in, 170
venous hamartoma in, 353
ventral spinal root degeneration in, 25
Wallerian degeneration in, 417, 418, 419
- Hound
ataxia in, 321, 322
epizootic peroneal and tibial neuropathy in, 446
idiopathic polyradiculoneuritis in, 424
Lafora body disease in, 327
leukodystrophy in, 283-284
globoid cell, 220
mucopolysaccharidosis in, 231
nervous system degeneration in, 322-323
vertebral malformation in, 200
- Human infectious mononucleosis, 143
- Human spongiform encephalopathy, 139-141
- Humpyback, 264, 266
- Hunter's disease, 230
- Hunting dog, 246
- Hurler's disease, 230
- Husky, 430, 450
- Husky-crossbreed racing sled dog, 450
- Hydranencephaly, 72-73
- Hydrocarbon insecticide poisoning, 256-257
- Hydrocephalus, 75-77
obstructive, 351, 352
- Hydrolase, 214
- Hydromyelia, 77-78
- Hyperammonemia, 210-211, 212
- Hyperchylomicronemia, 464
- Hyperglycinemia, 211
- Hypermnatremia, 255
- Hyperostosis, 356
- Hyperoxaluria, 465
- Hyperpipecolic acidemia, 214
- Hypertrophic astrocytes, 13
- Hypertrophic neuropathy, 421-422
canine inherited, 437-439
in horse, 440
- Hypertrophic polynuropathy, 439-440
- Hypertrophy
of blood vessels, 104
of ligamentum flavum, 199
- Hypoadrenocorticism, 246
- Hypochoeris radiata*, 450, 451
- Hypoderma bovis*, 162
- Hypoderma lineatum*, 162
- Hypoglycemia, 246
- Hypomyelination, 221, 281-282
in bovine virus diarrhea, 84, 85
in polyneuropathy, 441
- Hypomyelinogenesis, 287-295
congenital, 287-290, 293, 298
- Hypophysis, 380-384
- Hypoplasia
cerebellar, 25, 26, 301
of corpus callosum, 72
optic nerve, 78-79
prosencephalic, 68-69
- Hypothalamic hamartomas, 352
- Hypothyroid neuropathy, 462-463
- Hypothyroidism, 462-463
- Hypovitaminosis A, 271
- Hypoxia and ischemia, 237-249
anesthesia-related syndromes in, 241-242
cerebrovascular accidents in, 244
encephalomalacia in, 246
fibrocartilaginous embolic myelopathy in, 246-249
hypoglycemia in, 246
ischemic encephalopathy in, 242-244, 249
neonatal maladjustment syndrome in, 240-241

Hypoxia and ischemia—cont'd
seizures and cerebral necrosis in, 244-246

I

Ibiza Hound, 322-323

ICAM-1; *see* Intercellular adhesion molecule-1

Idiocy, 234

Idiopathic facial paralysis, 447-448

Idiopathic immune-mediated polyarteritis, 114-117

Idiopathic myenteric ganglionitis, 431

Idiopathic polyradiculoneuritis, 424-427

Iliac arterial embolism, 453

Immersion fixation, 29

Immune complex

disease of, 116

choroid plexus and, 19

in feline infectious peritonitis and equine infectious anemia, 116

Immune-mediated demyelination, 43

Immune-mediated diseases, 24

Immune-mediated polyarteritis, 114-117

Immunobiology, 23-25

Immunodeficiency virus encephalomyelitis, 122

Immunoglobulin index or quotient, 48

Immunoglobulin superfamily of adhesion molecules, 40

Immunohistochemistry, 29-30, 31

Immunological reactions, 11

Immunopathology, 23-25

Incisures, Schmidt-Lantermann; *see* Schmidt-Lantermann incisures

Inclusions

aging of, 51-52

crystalline, 405

cytoplasmic, 7

in canine distemper encephalitis, 104

in rabies, 96, 98

Joest-Degen, 149

neuronal, 7

osmiophilic, 414

tubuloreticular, 105, 106

ubiquitinated, 7

Infantile amaurotic idiocy, 234

Infantile spinal muscular atrophy, 308

Infarction, 237, 238, 239

cerebellar, 238, 244

cerebral, 244

hemorrhagic, 244

of optic nerve, 249

Infection

aerosol, 97

bacterial, 151

fungal, 151-155

inflammation and, 44-46

mycoplasma, 44, 45

rickettsial, 150-151

Infection—cont'd

spirochetal, 155-156

viral; *see* Virus

Infectious anemia, 146-148

immune complex formation in, 116

Infectious mononucleosis, 143

Infectious peritonitis, 116, 119

Infectious rhinotracheitis, 141

Inflammation, 39-47

defined, 95

demyelination in, 42-44

hallmarks of, 39-42, 43

infectious agents and, 44-46

neuroinvasiveness and neurovirulence in, 46-47

nonsuppurative, in rabies, 96, 97

Inflammatory diseases

of central nervous system, 95-188

adenovirus vasculitis in, 117, 118

arthritis encephalitis syndrome in, 128-129

Aujeszky's disease in, 100-102

bacterial infections in, 151

Borna disease in, 148-149

brain abscesses in, 156-159

coronavirus encephalomyelitis in, 149

demyelinating optic neuritis in, 122-123

distemper encephalomyelitis in, 102-110; *see also* Distemper encephalomyelitis

encephalitis in, 111-114, 115

encephalomyelitis in, 125-128

enterovirus encephalomyelitis in, 123-125

fungal infections in, 151-155

granulomatous meningoencephalomyelitis in, 110-111, 112, 113

herpesvirus 1 encephalomyelopathy in, 146, 147

herpesvirus encephalomyelitis in, 117

herpesvirus meningoencephalomyelitis in, 141

immunodeficiency virus encephalomyelitis in, 122

infectious anemia in, 146-148

infectious peritonitis in, 119

listeriosis in, 133-135

louping ill in, 132-133

malignant catarrhal fever in, 142-143

meningitis in, 156-159

meningoencephalomyelitis in, 114-117, 141

Newcastle disease in, 118

parainfluenza virus in, 117-118

parasitic encephalomyelitis in, 159-162, 163

polioencephalomyelitis in, 119-122

Inflammatory diseases—cont'd

of central nervous system—cont'd

protozoan encephalomyelitis in, 162-171; *see also* Protozoan encephalomyelitis

pyogranulomatous meningoencephalomyelitis in, 118-119

rabies in, 95-100

rickettsioses in, 150-151

scrapie in, 136-139

spirochetal infections in, 155-156

sporadic encephalomyelitis in, 144

thrombotic meningoencephalitis in, 143-144

transmissible encephalopathies in, 139-141

viral encephalomyelitis in, 144-146

visna in, 129-132

ependymal cells and, 19

of peripheral nervous system, 424-437

brachial plexus neuritis in, 427-428

cauda equina neuritis in, 432, 433-434

cranial neuritis in, 436-437

enteric ganglionitis in, 431

ganglioradiculitis in, 428-431

granulomatous radiculitis in, 436

polyradiculoneuritis in, 424-427

protozoan polyradiculoneuritis in, 434-436

Inflammatory response, 23

Inherited congenital myoclonus, 297

Inherited congenital tetany, 298

Inherited hypertrophic neuropathy, 437-439

Inherited neuronal dystrophy, 464

Injection injury, 455

Injury, 189-207

blindness and optic nerve degeneration in, 193-204

calcinosis circumscripta in, 204-205

injection, 455

neuronal, 237-238

reperfusion, 237

spinal cord, 193-204; *see also* Spinal cord injuries

traumatic, 189-193

Inner mesaxon, 405

Insecticide poisoning, 256-257

Insulinoma, 472-473

Integrins, 40

Intercellular adhesion molecule-1, 40

Internal capsule, 25, 26

Internodes, 12

intercalated, 421

Intervertebral disk disease, 202-204

Intoxication, 250-271; *see also* Poisoning

Intracranial germinoma, 385

Intradural-extramedullary spinal cord tumors, 386-391

- Intrahepatic shunts, 208
 Intraperiod dense line, 14
 Intraperiod line, 404
 Intracellular germ cell tumors, 384-385
Iridovirus, 126
 Irish Setter
 cerebellar malformations in, 85
 lissencephaly in, 74
 polyneuropathy in, 473
 Ischemia, 237-249; *see also* Hypoxia and ischemia
 Ischemic cell change, 239
 Ischemic neuromyopathy, 249
 feline, 453
 Ischemic neuron, 239-240
 in distemper encephalitis, 104
 ISMA; *see* Infantile spinal muscular atrophy
 Isomorphic gliosis, 41
 Isomorphic pinal tumor, 379
 Ivermectin poisoning, 266-267
Ixodes ricinus, 132
- J**
- Jack Russell Terrier
 ataxia and myelopathy in, 321
 myelin ballooning in, 406
 sensory neuropathy in, 444
 Japanese encephalitis, 146
 Japanese Macaque, 301
 Japanese Spaniel, 218
 Javelinas, 102
 Jersey calf
 hypomyelination in, 290, 299
 megalencephaly in, 75
 Jimmy fern, 263
 Jimmy mouse, 294
 Joest-Degen inclusion bodies, 149
- K**
- Kangaroo gait, 452-453
 Karnovsky's fixation, 29
Karwinskia humboldtiana, 469
 Karyorrhexis, 100
 Kelpie, 301, 302
 Kernohan's grading of astrocytomas, 363
 Kerry-Blue Terrier, 301, 302-303
 Ketoacid decarboxylase deficiency, 297-298
 Kinesin, 403
 Kitten; *see also* Cat
 hydranencephaly in, 73
 hydrocephalus in, 77
 metabolic disorders in, 213
 microphthalmia in, 79
 optic nerve hypoplasia in, 79
 Knapweed, 263
 Kolmer cells, 19
 Kooiker dog, 324
- Krabbe's disease
 in Cairn Terrier, 306
 central nervous system and, 220
 peripheral nervous system and, 458-459
 Kudu, 139
 Kufs disease, 234
 Kugelberg-Welander syndrome, 308
 Kuru, 139-141
- L**
- Labrador Retriever
 axonopathy in, 323-324
 cerebellar cortical abiotrophy in, 301
 corpus callosum aplasia in, 72
 fibrocartilaginous embolic myelopathy in, 248
 leukodystrophy in, 282-283
 spongy degeneration in, 295
 Laceration, 190, 191, 192
 LaCrosse virus, 146
 Lafora bodies, 7
 aging changes in, 52
 Lafora body disease, 327
 Lamb; *see also* Sheep
 Arnold-Chiari malformation in, 81-82
 Border disease in, 288-290
 cerebellar cortical abiotrophy in, 305
 congenital hypomyelinating neuropathy in, 441
 copper deficiency in, 273-276
 daft disease of, 305
 Dandy-Walker syndrome in, 86
 fibrocartilaginous embolic myelopathy in, 249
 focal symmetrical encephalomalacia in, 269-270
 holoencephaly in, 72
 leptomeningitis in, 156
 medullary dysplasia in, 79
 mesangiocapillary glomerulonephritis in, 116
 neuroaxonal dystrophy in, 316-317
 plant poisoning in, 265-266
 porencephaly in, 73
 vertebral body abscesses in, 158
 vertebral fracture in, 192
 Lamellar bodies, 97, 98
 Laminar cortical necrosis, 104
 Lapland reindeer-herd dog
 glycogenesis in, 232
 neuronal abiotrophy in, 306-309
 Laryngeal hemiplegia, 448-450
 Laryngeal nerve, left recurrent, 448
 Laryngeal paralysis, 450-451
 Laurel, 263
 Lead
 demyelination and, 421
 poisoning with
 central nervous system and, 250-252
 cont'd
 poisoning with—cont'd
 peripheral nervous system and, 465-466
 Leaner gait, 305
 Leight's disease, 212
 Leopard, 102
 Leptomenigeal arteries, 116
 Leptomeninges, 52-53
 Leptomeningitis, 156, 157, 158
 in feline infectious peritonitis, 119, 121
 Lesions
 in Aujeszky's disease, 102
 in brain, 28
 cystic, 354
 demyelinating, 25
 diseases without, 35-36
 in granulomatous meningoencephalomyelitis, 111
 malformative vascular, 352-353, 354
 in Pug dog encephalitis, 111-114
 in spinal cord, 28
 traumatic, 415
 Leukemia virus, 313
 Leukocyte extravasation, 40
 Leukocyte infiltration, 424-425
 Leukodystrophy, 215, 281, 282-287
 globoid cell
 in Cairn Terrier, 306
 central nervous system and, 220-221, 222, 223
 peripheral nervous system and, 458-459
 Leukoencephalitis, 110
 Leukoencephalomalacia, 270-271
 Leukoencephalomyeloneuropathy, 452
 Leukoencephalomyelopathy, 285
 Levamisole, 258
 Lewy bodies, 7
 LFB stain; *see* Luxol fast blue stain
 Lhasa Apso
 lissencephaly in, 74
 lumbosacral stenosis in, 454
 Ligamentum flavum, 199
 Limb monoparesis, 446
 Limber leg, 469
 Limousin calf, 326-327
 Lion, 102
 Lipids, 404
 Lipofuscin, 7
 accumulation of, 411
 aging changes in, 52
 in glycogenesis, 233
 Lipoma, 354, 355
 Lipomeningocele, 71, 86
 Lissencephaly, 73-74
 Listeriosis, 133-135
 Llama, 277
 LMN disease; *see* Lower motor neuron disease

- Locoweeds, 227
 Lolitrems, 261
Lolium perenne, 261
 Louping ill, 132-133, 146
 Lower motor neuron disease
 in cats, 312
 in dogs, 308
 in mice, 312-313
 neurofibrillary accumulation in, 313-315
 Lumbar root of sciatic nerve, 457
 Lumbosacral stenosis, 454
 Lupus, 116
 Lurcher gait, 305
 Lurcher puppy, 293
 Lusc bodies, 474
 Luxol fast blue stain, 29, 30, 423
 Lyme disease, 155
 Lymphocytes
 in distemper encephalitis, 104
 in ganglioradiculitis, 430
 in radiculitis, 429, 430
 in vasculitis, 142
 Lymphoid neoplasia, 481
 Lymphoma, 393, 394
 central nervous system, 379, 380
 Lysosomal storage disease, 214-237
 ceroid-lipofuscinosis in, 233-236
 cytoplasm in, 7
 genetics in, 214-216
 glycogenosis in, 231-233
 glycoproteinosis in, 224-230
 mucopolysaccharidosis in, 230-231
 principles of, 214-218
 sphingolipidoses in, 218-224, 225
- M**
 Macaque, 301
 Macroglia, 42
 Macroglial cells, 2-3
 Macrophage, 19-23
 in distemper encephalitis, 105
 in ganglioradiculitis, 430
 myelin and, 17
 in Wallerian degeneration, 9
 MAG; *see* Myelin-associated glycoprotein
 Main Drain virus, 146
 Major dense line, 14, 404
 Major histocompatibility complex, 22-23
 Malacia, 23, 24
 Malamute, 441-442
 Malarticulation, cervical vertebral, 198-199, 200, 201
 Malformation, 68-94
 brain, 68-86; *see also* Brain
 central nervous system, 352-355
 cervical vertebral, 198-199, 200, 201
 occipitoatlantoaxial, 198
 spinal cord, 86-90
 spinal cord injury and, 193-202; *see also* Spinal cord injuries
 Malignant astrocytoma, 363, 364
 Malignant catarrhal fever, 142-143
 Malignant ependymoma, 375
 Malignant germ cell tumor, 385
 Malignant melanoma, 393
 Malignant oligodendroglioma, 372-373
 Malignant peripheral nerve sheath tumor, 476, 477, 478
 Malinois Shepherd-cross puppy, 300
 Maltese Terrier, 263
 Malva parviflora, 451
 Mannosidosis, 226-230
 caprine and feline, 460
 Manx cat, 87-88
 Maple syrup urine disease, 211, 297-298
 Marek's disease, 481
 Maroteaux-Lamy disease, 230, 231
 Mast cells, 409
 Mastiff
 hypertrophic neuropathy in, 437-439
 polyradiculoneuritis in, 422
 spongy degeneration in, 299
 MCB; *see* Membranous cytoplasmic bodies
 MCF; *see* Malignant catarrhal fever
 Medulla, 2
 malformations in, 79-82
 meningioma of, 359
 Medulloblastoma, 378-379
 Medulloepithelioma, 380
 Megalocephaly, 74-75
 Melanin, 33-34
 Melanocytes, 34
 Melanoma, 393
 Membranous cytoplasmic bodies, 219, 220
 Meningeal hemorrhage, 191
 Meningeal polyarteritis, 114
 Meningeal tumor, 355-362; *see also* Meningioma
 Meningeal vasculitis, 142
 Meninges, 3
 Meningioangiomatosis, 353-354
 Meningioma, 355-362
 angioblastic, 359, 360
 in cats, 361, 362
 in dogs, 361
 falx, 356, 357
 fibroblastic, 358, 360
 medullary, 359
 meningothelial, 356-360
 in mice and rats, 362
 microcystic, 359, 360
 papillary, 358
 psammomatous, 359, 360
 syncytial, 356-360
 transitional, 358, 360
 Meningitis, 156-159
 Meningocele
 in brain malformations, 69-71
 in spinal cord malformations, 86
 Meningocerebral hemangiomatosis, 354
 Meningoencephalitis, 156
 amebic, 170
 bacterial, 134
 thrombotic, 143-144
 Meningoencephalocle, 69-71
 Meningoencephalomyelitis, 114-117, 156
 bovine herpesvirus, 141
 granulomatous, 110-111, 112, 113
 pyogranulomatous, 118-119
 sporadic, 141
 Meningomyelocele, 86, 88
 Meningothelial meningioma, 356-360
 Menkes' disease, 277
 Mercaptans, 211
 Mercury poisoning
 central nervous system and, 253-254
 peripheral nervous system and, 466-467
 Merino sheep
 cerebellar cortical abiotrophy in, 301, 305
 myelopathy in, 324-325
 neuroaxonal dystrophy in, 317
 Mesangiocapillary glomerulonephritis, 116
 Mesaxon, 405
 Mesencephalon, 2
 malformations in, 79
 Metabolic acidosis, 212
 Metabolic disorders
 of central nervous system, 208-249
 hepatic and renal encephalopathy in, 208-211
 hypoxia and ischemia in, 237-249; *see also* Hypoxia and ischemia
 intermediary, 211-214
 lysosomal storage disease in, 214-237; *see also* Lysosomal storage disease
 of peripheral nervous system, 458-465
 diabetic neuropathy in, 462
 fucosidosis in, 459-460
 gangliosidosis in, 461-462
 globoid cell leukodystrophy in, 458-459
 hyperchylomicronemia in, 464
 hyperoxaluria in, 465
 hypothyroid neuropathy in, 462-463
 inherited neuronal dystrophy in, 464
 mannosidosis in, 460
 Niemann-Pick disease polyneuropathy in, 460-461
 pantothenic acid deficiency in, 463
 riboflavin deficiency in, 463-464
 Metabolic megalencephaly, 74
 Metabolites, arachidonic acid, 38
 Metachromatic leukodystrophy, 221, 281
 Metaplasia, 52
 Metastatic central nervous system tumors, 391-394
 Metencephalon, 2

- Methenamine silver, 30
 Methylmercury poisoning, 467
 Metronidazole poisoning, 267
 MHC; *see* Major histocompatibility complex
 Mice; *see* Mouse
 Microcystic meningioma, 359, 360
 Microencephaly, 74
 Microglial cells, 2-3, 19-23
 in canine distemper encephalitis, 104
 in gliosis, 42
 Microgliomatosis, 380, 381
 Microgliosis, 3
 Microphthalmia, 78-79
 Microscopy, electron, 29
 Microtubules, 402-403
 Microvasculature, 23, 24
 Midbrain, 2
 Mineralization, 53
 Miniature dogs, 246
 Miniature Poodle
 atlantoaxial subluxation in, 201
 demyelinating disease in, 284-285
 globoid cell leukodystrophy in, 220
 neuronal abiotrophy of, 307
 Niemann-Pick disease in, 224
 optic nerve hypoplasia in, 79
 Miniature rabbit, 283
 Mink
 distemper encephalomyelitis in, 102
 encephalopathy in, 139, 140
 hemivertebra in, 201
 metachromatic leukodystrophy in, 221
 thiamine deficiency in, 280
 vitamin A deficiency in, 271
 Minor dense line, 14
 Mitochondria, 403-404, 411
 crystalline inclusions in, 405
 Mitochondrial diseases, 214
 MLD; *see* Metachromatic leukodystrophy
 Mold, 262
 Molecular biology, 30-32
 Mongrel, 301
 Monkey; *see also* Primate
 cerebrovascular accidents in, 244
 ceroid-lipofuscinosis in, 236
 mycotoxic peripheral myelinopathy in, 468-469
 senile plaque in, 54
 Monkey face, 72
 Mononuclear cells
 in distemper encephalomyelitis, 103
 in meningoencephalomyelitis, 111
 Mononucleosis, human infectious, 143
 Monoparesis, 446
 Morbillivirus, 102
 Morgan horse, 317
 Mosquito, 145
 Motor neuron, 412-413
 Motor neuron disease, 307-315
 Motor neuron disease—cont'd
 in cats, 312
 cytoplasmic inclusions in, 7
 in dogs, 308
 in horses, 309-311
 in mice, 312-313
 neurofibrillary accumulation in, 313-315
 Mountain laurel, 263
 Mouse
 aging changes in, 51
 astrocytoma in, 369
 axonal reaction in, 416
 cerebellar cortical abiotrophy in, 301
 coronavirus encephalomyelitis in, 149
 encephalitozoonosis in, 169
 epidermoid cysts in, 355
 focal symmetrical encephalomalacia in, 269-270
 globoid cell leukodystrophy in, 221
 hydrocephalus in, 77
 hypomyelination in, 294
 hypomyelination congenita in, 293-294
 inherited cerebellar disorders in, 305
 leukemia virus in, 313
 meningioma in, 362
 Menkes' disease in, 277
 motor neuron disease in, 312-313
 neuronal abiotrophy of, 307
 neuronal aging in, 49-50
 Niemann-Pick disease in, 224
 scrapie in, 137-138
 spongy degeneration in, 299
 Theiler's disease in, 124-125
 thiamine deficiency in, 280
 toxoplasmosis in, 169
 MPNST; *see* Malignant peripheral nerve sheath tumor
 MPS; *see* Mucopolysaccharidosis
 MS; *see* Multiple sclerosis
 MSUD; *see* Maple syrup urine disease
 Mucocytes, 35, 36
 Mucopolysaccharidosis, 216, 230-231
 Mucor, 151
 Mucormycosis, 152
 Mule deer, 139
 Multilobular osteochondroma, 391
 Multiple cartilaginous exostosis, 201-202, 391
 Multiple myeloma, 393
 Multiple sclerosis, 16, 43
 Murine; *see* Mouse; Rat; Rodent
 Murine model of Sly syndrome, 231
 Murray Grey cattle
 mannosidosis in, 226
 polymicrogyria in, 74
 progressive encephalomyelopathy in, 325
 Murray Valley encephalitis, 146
 Murrurundi disease, 299
 Muscle weakness and wasting, 461-462
 Muscular atrophy, 308-309, 314
 Mustelidae, 102
 Mycoplasma infections, 44, 45
 Mycosis, guttural pouch, 436-437
 Mycotic encephalitis, 152, 153
 Mycotoxic peripheral myelinopathy, 468-469
 Myelencephalon, 2
 Myelin
 aging change in, 406
 artifact of, 422-423
 axons and, 404
 blebbing of, 406
 deficiency of, 294-295
 injury to, 108-110
 oligodendrocytes and, 12
 phagocytosis of, 44
 protein of, 15
 in hypertrophic neuropathy, 439
 Myelin-associated glycoprotein, 15, 405
 Myelin bodies, 405
 Myelin ovoid, 417
 Myelin sheaths, 439
 Myelination, 14-16
 Myelinopathy
 mycotoxic peripheral, 468-469
 progressive spinal, 325
 Myelitis
 in Aujeszky's disease, 102
 protozoal, 25
 Myelodysplasia, 88-90
 Myeloencephalopathy, degenerative, 317-319
 paresis and ataxia in, 193
 progressive, 325
 vitamin E deficiency in, 273
 Myeloid neoplasia, 481
 Myeloma, multiple, 393
 Myelomalacia, 191
 in intervertebral disk disease, 203, 204
 Myelopathy
 cervical stenotic, 193-198
 degenerative, 319-321
 equine herpesvirus, 146, 147
 fibrocartilaginous embolic, 246-249
 hemorrhagic, 241-242
 in Kooiker dogs, 324
 in Merino sheep, 324-325
 stenotic, 193-198
 in Terriers, 321-322
 traumatic feline ischemic, 249
 Myelorradiculitis, 166
 Myenteric ganglionitis, 431
 Myoclonia congenita, 290-291
 Myoclonus
 in canine distemper, 103
 congenital, 297
 Myopathy, 242
 Myxopapillary ependymoma, 375

N

- NAD; *see* Neuroaxonal dystrophy
- Nageotte nodule, 412
- Nanophyetus salminicola*, 151
- Nauta-Gygax technique, 29, 30
- NCE; *see* Neuritis of cauda equina
- Necrosis
- in cavitation, 24
 - cerebral, 242, 244-246
 - cerebrocortical, 277-280
 - in cyst formation, 24
 - internal capsule, 25, 26
 - laminar cortical, 104
 - neuronal, 25
 - toe or paw, 442
- Necrotizing encephalomyelopathy, 212
- Negri bodies, 96, 98
- Neguvon; *see* Trichlorfon
- Neonatal adrenoleukodystrophy, 214
- Neonatal maladjustment syndrome, 240-241
- Neoplasia; *see* Tumors
- Neoplastic reticulosis, 111
- Neorickettsia helminthoeca*, 151
- Neospora*, 163-169
- Neospora caninum*, 163, 435-436
- Nerve
- compression of, 242
 - entrapment of, 458
 - femoral, 457-458
 - fibers of, 402, 410
 - granulomatous radiculitis of, 436
 - injury to, 455
 - left recurrent laryngeal, 448
 - obturator, 457
 - optic; *see* Optic nerve
 - radial, 452-453
 - sciatic, 457
 - suprascapular, 458
 - trigeminal, 475
 - vestibulocochlear, 436
- Nerve growth factor, 403, 418
- Nervous gait, 305
- Neural pacemaker nodule, 456
- Neural plate, 1
- Neural tube, 2
- Neuraxial edema, 297
- Neurifibroma, 474-475
- Neurilemma, 473
- Neurilemmoma, 473
- Neurinoma, 473
- Neuritic plaque, 54, 55
- Neuritis
- allergic, 421
 - brachial plexus, 427-428
 - of cauda equina, 405-406, 432, 433-434
 - cranial, 436-437
 - optic, 122-123
- Neuroaxonal dystrophy, 8-9, 315-317
- Neurocytoma, 375, 377
- Neuroectodermal tumor, 364, 375, 378-379
- Neuroendocrine cells, 414
- Neurofibrils, 54, 313-315, 402
- Neurofibroma, 473, 474
- Neurofibromatosis, 474, 476-481
- Neurofibrosarcoma, 473, 475
- Neurofilaments, 8-9
- peripheral nervous system, 403
 - peripherin, 416
- Neurogenic muscular atrophy, 308-309
- Neuroglia, 2-3
- Neurohypophysis tumor, 384
- Neuroinvasiveness, 46-47
- Neurokeratin network, 423
- Neurological disorder, 103; *see also* Central nervous system; Peripheral nervous system
- Neuroma, 455-457, 473
- Neuromelanin, 7, 34
- Neuromyopathy, ischemic, 249
- feline, 453
- Neuron, 2-10
- aging of, 49-50
 - anatomy of, 4
 - appearance of, 33
 - central nervous system, 2-3
 - dark, 35
 - degeneration of, 4-5
 - in Aujeszky's disease, 100
 - hereditary porcine, 306
 - dystrophy of, 464
 - encrustation of, 7
 - formation of, 1-2
 - function of, 4-7
 - in gangliosidosis, 218, 219
 - glycoproteinosis of, 52, 327
 - granule cell, 34
 - injury to, 237-238
 - ischemic, 239-240
 - in distemper encephalitis, 104
 - loss of, 54
 - motor, 307-315; *see also* Motor neuron disease
 - necrosis of
 - in Aujeszky's disease, 101
 - in ventral horn of spinal cord, 25
 - of peripheral nervous system, 410-414
 - Purkinje, 35
 - in gangliosidosis, 218, 219
 - somatic motor, 412-413
 - of spinal ganglia, 410-411
 - tumors of, 375-378
 - in Wallerian degeneration, 9-10
- Neuronal abiotrophy, 300-307
- Neuronal cell bodies, 410, 411
- Neuronal ceroid-lipofuscinosis, 233-236
- Neuronal inclusions, 7
- Neuronal satellites, 20, 21
- Neuronal satellitosis, 39-40, 42, 43
- Neuronophagia, 3
- in ganglioradiculitis, 429, 430
 - inflammation and, 42, 43
- Neuropathogenic virus, 44
- Neuropathy
- diabetic, 462
 - dying back, 420-421
 - epizootic peroneal and tibial, 446
 - in German Shepherd, 446-447
 - giant axonal, 444-445
 - hereditary sensory, 442-443
 - in hyperoxaluria, 465
 - hypertrophic, 421-422
 - canine inherited, 437-439
 - focal trigeminal, 440
 - hypothyroid, 462-463
 - in inherited hyperchylomicronemia, 464
 - in insulinoma, 472-473
 - onion bulb, 440
 - paraneoplastic, 472
 - sensory, 428-431
 - in longhaired Dachshunds, 443-444
 - vincristine, 468
- Neuropathy target esterase, 256
- Neuropraxia, 415
- Neuroschisis, 69
- Neurotmesis, 415
- Neurotoxic esterase, 256
- Neurotransmitters, 237-238
- Neurotrophic factor, 403, 418
- Neurovirulence, 46-47
- Neutrophil infiltrate, 119
- Newcastle disease virus, 117-118
- NGF; *see* Nerve growth factor
- Niemann-Pick disease, 215, 223-224, 225
- feline, 460-461
- Nigropallidal encephalomalacia, 263-264
- Nissl bodies, 4
- chromatolysis and, 415
- NMS; *see* Neonatal maladjustment syndrome
- Nodes
- ectopic neural pacemaker, 456
 - nageotte, 412
 - of Ranvier, 12, 404
 - Schmorl's, 202, 248-249
- Nonchondrodystrophic breeds of dogs, 202
- Nonsuppurative inflammation, 96, 97
- Norwegian forest cat, 232-233
- Nose, carcinoma of, 391-393
- Nosema*, 169
- Notholaena sinuata*, 263
- Nubian goat
- ceroid-lipofuscinosis in, 234, 236
 - mannosidosis in, 228
 - Sanfilippo disease in, 231
- Nuclear bodies, 106
- Nucleus
- of astrocytes, 11-12
 - of microglial cells, 20

- Nucleus—cont'd
 olivary, 33
 Nutritional disorders
 of central nervous system, 271-280
 copper deficiency in, 273-277
 thiamine deficiency in, 277-280
 vitamin A deficiency in, 271-272
 vitamin E deficiency in, 272-273
 of peripheral nervous system, 458-465
 diabetic neuropathy in, 462
 fucosidosis in, 459-460
 gangliosidosis in, 461-462
 globoid cell leukodystrophy in, 458-459
 hyperchylomicronemia in, 464
 hyperoxaluria in, 465
 hypothyroid neuropathy in, 462-463
 inherited neuronal dystrophy in, 464
 mannosidosis in, 460
 Niemann-Pick disease in, 460-461
 pantothenic acid deficiency in, 463
 riboflavin deficiency in, 463-464
 Nyala, 139
- O**
- OAA; *see* Occipitoatlantoaxial malformation
- Obstructive hydrocephalus, 75, 77
 central nervous system tumors and, 351, 352
- Obturator nerve, 457
- Occipitoatlantoaxial malformation, 198
- Odocoileus virginianus*, 159
- Old animals, 49-55
 degenerative myelopathy of, 319-321
 encephalitis of, 110
 myelin of, 406
- Oligodendroblast, 3
- Oligodendrocyte, 3, 4, 10-18
 in canine distemper encephalitis, 108
 in central nervous system injury, 11-18
 formation of, 2
 in immunological reactions, 11
 roles of, 10-11
- Oligodendroglia, 4
 dysplasia of, 287
 tumors of, 370-373
- Olivary nucleus, 33
- Olivopontocerebellar atrophy, 306
- Onion bulb, 4
 in horse, 440
 in hypertrophic neuropathy, 439, 440
 in laryngeal hemiplegia, 449, 450
 in segmental demyelination, 421, 422
- Ontario encephalomyelitis, 127
- Optic nerve
 degeneration of, 204
 glioblastoma of, 367
 hypoplasia of, 78-79
 infarction of, 249
- Optic neuritis, 122-123
- Optic vesicles, 2
- Orbivirus, 73
- Ordinary stringhalt, 451
- Organoarsenicals, 252
- Organomercury poisoning, 253-254
- Organophosphate poisoning, 255-256
- Oryx, 139
- Osmiophilic inclusions, 414
- Osmium fixation, 423
- Osseous metaplasia, 52
- Osteochondrosarcoma, 391
- Otitis media, 158, 159
- Otter, 102
- Outer mesaxon, 405
- Oxygen-free radicals, 38
- Oxytropis*, 227-228
- P**
- Pacemaker nodule, 456
- Pachygyria, 73-74
- Pachymeningitis, 156, 157, 158
- Panda, 102
- Panleukopenia virus, 73, 82-83
- Pantothenic acid deficiency, 463
- Papillary meningioma, 358
- Papilloma, 352, 374
- Paraformaldehyde fixation, 29
- Paraganglionic cells, 414
- Parainfluenza virus, 117-118
- Paralysis
 calving, 457
 Chastek, 280
 coonhound, 424, 426
 curled toe, 463-464
 facial, 436
 femoral nerve, 457-458
 idiopathic facial, 447-448
 laryngeal, 450-451
 in rabies, 96
 sphincter, 433
 Stockard's, 308
 tail, 433
 transient, 38
- Paramyxovirus, 117, 128
- Paraneoplastic neuropathy, 472
- Paraneoplastic syndromes, 36
- Parasitic encephalomyelitis, 159-162, 163
- Parelaphostrongylus tenuis*, 159-160
- Paresis, 123, 193; *see also* Paralysis
- Parkinsonism, 7
- Parrot, 370
- Pars distalis of pituitary, 380-384
- Parvovirus, 82-83
- Paspalum staggers, 262-263
- Pasteurella multocida*, 158
- Paw necrosis, 442
- PDGF; *see* Platelet-derived growth factor
- Pedigree analysis, 216
- Pekingese
 intervertebral disk disease in, 202
 vertebral malformation in, 200
- Pelizaeus-Merzbacher disease, 281
- Pelvic limb monoparesis, 446
- PEM; *see* Polioencephalomalacia
- Penicillium*, 261, 262
- Peptides, 411
- Perennial ryegrass staggers, 261
- Perfusion, vascular, 29
- Perichiasmatic germ cell tumor, 385
- Perikarya, sensory, 411-412
- Perikaryon, 4, 5
- Perineurioma, 473, 474
- Perineurium, 407-408, 410, 439
- Peripheral myelin protein 22, 439
- Peripheral nerve
 compression of, 242
 injection injuries to, 455
- Peripheral nervous system, 402-501
 artifacts in, 422-423
 components of, 402
 degenerative diseases of, 437-453; *see also* Degenerative diseases
 inflammatory diseases of, 424-437; *see also* Inflammatory diseases
 metabolic disorders of, 458-465; *see also* Metabolic disorders
 neoplasia of, 472-481; *see also* Tumors
 pathology of, 414-422
 axonal degeneration and regeneration in, 420
 axonal reaction in, 415-417
 distal axonopathy in, 420-421
 segmental demyelination in, 421-422
 traumatic lesions in, 415
 Wallerian degeneration in, 417-420
 poisoning of, 465-471; *see also* Poisoning
 traumatic lesions of, 415, 453-458
 tumors of, 472-481; *see also* Tumors
- Peripherin, 403, 416
- Peritonitis, 116, 119
- Perivascular cells, 20
- Perivascular cuffing, 39-40, 41
 in distemper encephalitis, 104
- Peroneal neuropathy, 446
- Peroxisomal disorders, 213-214
- Persian cat, 227
- Pestivirus, 83
- Phaeohyphomycoses, 155
- Phagocytic activities of macrophages, 23
- Phagocytosis, 44
- Phalaris staggers, 7, 263
- Phenylketonuria, 211
- Phosphoprotein, 418
- Pi granules, 405
- Pia mater, 3
- Pick's disease, 7

Pig

- astrocytomas in, 369
- Aujeszky's disease in, 100, 101, 102
- cerebellar cortical abiotrophy in, 301
- cerebellar disc in, 305
- cerebrovascular accident in, 244
- cholera in, 125-126
- copper deficiency in, 276
- edema disease in, 267
- encephalocele and meningocele in, 69
- encephalomyelitis in, 125-128
- enterovirus infection in, 123
- fibrocartilaginous embolic myelopathy in, 247, 249
- ganglionitis in, 125
- gangliosidosis in, 218
- holocephaly in, 72
- hypomyelination in, 290-291
- hypovitaminosis A in, 272
- leptomeningitis in, 156, 157
- malformations in
 - cerebellar, 84
 - cyclopic, 71
- medulloblastomas in, 378
- neuronal system degeneration in, 306
- otitis media in, 158, 159
- pantothenic acid deficiency in, 463
- poisoning in
 - arsenic, 252-253
 - insecticide, 256
 - mercury, 253
 - organophosphate, 255
 - salt, 254, 255
- poliomyelomalacia in, 258-260
- rabies in, 96
- salmonellosis in, 151
- spinal muscular atrophy in, 314, 315
- toxoplasmosis in, 169
- tremorgenic syndromes in, 262
- vesicular disease in, 127-128
- vitamin A deficiency in, 271

Pigeon, 118

Pigment, 7, 52

Pilocytic astrocytoma, 363

Piloid astrocytoma, 363

Pineal tumor, 379

Pineoblastoma, 379

Pineocytoma, 379

Pituicytoma, 384

Pituitary abscess, 158

Pituitary gland tumor, 380-384

Plants

- in ceroid-lipofuscinosis, 236
- in mannosidosis, 227-228
- poisoning from, 265-266
- in tremorgenic syndromes, 263

Plaque, 54, 55

Plasma cell

- in distemper encephalitis, 104
- in infectious peritonitis, 119

Platelet-derived growth factor, 10

Pleomorphic xanthoastrocytoma, 364

Plott hound, 231

PLP; see Proteolipid protein

PMP 22; see Peripheral myelin protein 22

PNET; see Primitive neuroectodermal tumor

PNS; see Peripheral nervous system

Pointer dog

gangliosidosis in, 218

hereditary sensory neuropathy in, 442-443

meningoencephalomyelitis in, 118-119

progressive neurogenic muscular atrophy in, 308-309

thoracic hemivertebra in, 200

Poisoning

of central nervous system, 250-271

arsenic in, 252-254

Astragalus in, 266

carbon monoxide in, 267

Chrysocoma tenuifolia in, 265-266

copper in, 211

cyanide in, 267

cycad in, 264-265

edema disease in, 267-269

ethylene glycol in, 257-258

focal symmetrical encephalomalacia in, 269-270

furazolidone in, 267

hexachlorophene in, 258

humptyback in, 266

insecticides in, 256-257

ivermectin in, 266-267

lead in, 250-252

leukoencephalomalacia in, 270-271

levamisole in, 258

mercury in, 253-254

metronidazole in, 267

nigropallidal encephalomalacia in, 263-264

organophosphates in, 255-256

poliomyelomalacia in, 258-261

rodenticides in, 267

salmon in, 151

salt in, 254-255

selenium in, 258-261

solanum in, 264, 265

Sorghum in, 266*Styandra* in, 266

tremorgenic syndromes in, 261-263

water in, 254

of peripheral nervous system, 465-471

acrylamide in, 421

autonomic disorders in, 469-471

coyotillo polynuropathy in, 469

lead in, 465-466

mercury in, 466-467

mycotoxic myelinopathy in, 468-469

pyridoxine in, 467-468

Poisoning—cont'd

of peripheral nervous system—cont'd

thallium in, 466

vincristine neuropathy in, 468

Polar bear, 13

Polar spongioblastoma, 380

Polioencephalomalacia, 245-246, 277-280

Polioencephalomyelitis, 119-122

Poliomyelitis suum, 123

Poliomyelomalacia, 24, 258-261

Polled Hereford cattle

cerebellar cortical abiotrophy in, 301

polymicrogyria in, 74

Polyarteritis, 114-117

Polyglucosan bodies, 52, 327

Polygonal neuroendocrine cells, 414

Polymicrocavitation, 209

Polymicrogyria, 74

Polyncuritis equi, 433

Polyneuropathy

congenital hypomyelinating, 441

coyotillo, 469

hereditary, 441-442

hypertrophic, 439-440

hypothyroidism and, 463

Niemann-Pick disease, 460-461

in Rottweiler, 445-446

Polyradiculoneuritis

canine and feline, 422

chronic, 427

idiopathic, 424-427

protozoan, 434-436

Pomeranian

atlantoaxial subluxation in, 201

globoid cell leukodystrophy in, 220

hypoglycemia in, 246

Pompe's disease, 231

Pons, 2

malformations in, 79

Pontomedullary meningioma, 356

Pony

cerebellar cortical abiotrophy in, 301, 305

Renaut bodies of, 409

Poodle

atlantoaxial subluxation in, 201

demyelinating disease in, 284-285

globoid cell leukodystrophy in, 220

hypoglycemia in, 246

Lafora body disease in, 327

lumbosacral stenosis in, 454

neuronal abiotrophy in, 307

Niemann-Pick disease in, 224

optic nerve hypoplasia in, 79

polymicrogyria in, 74

Porcine; see Pig

Porencephaly, 72-73

Porpoise, 102

Portosystemic shunts, 208

Portuguese water dog, 218

- Postanesthetic hemorrhagic myelopathy, 241-242
- Postanesthetic cerebral necrosis, 242
- Postanesthetic myopathy, 242
- Postneurectomy neuroma, 457
- Postvaccinal canine distemper encephalitis, 110
- Poultry; *see* Chicken; Goose; Turkey
- Powassan, 146
- Prairie dog, 160
- Preganglionic sympathetic neurons, 413
- Primate; *see also* Monkey
cerebellar cortical abiotrophy in, 301
cerebellar disease in, 305
ceroid-lipofuscinosis in, 234
distemper encephalomyelitis in, 102
encephalitozoonosis in, 170
- Primitive neuroectodermal tumor, 375, 378-379
- Prion protein, 138
- Procyonidae, 102
- Progenitor, 10
- Progressive ataxia, 286-287
- Progressive axonopathy, 445
- Progressive degenerative myelocneuropathy, 325
- Progressive neurogenic muscular atrophy, 308-309
- Progressive spinal myelinopathy, 325
- Prosencephalic hypoplasia, 68-69
- Prosencephalon, 2
- Prostatic carcinoma, 393
- Protein, 404
activator, 214
in canine distemper encephalomyelitis, 103
glial fibrillary acidic, 10
myelin, 15, 439
prion, 138
- Proteinosis, 52, 233
- Proteolipid protein, 15
- Proteolipid proteinosis, 52, 233
- Proteolysis, 17
- Protoplasmic astrocytes, 10
- Protoplasmic astrocytoma, 363
- Prototheca*, 156
- Protozoal myelitis, 25
- Protozoan encephalomyelitis, 162-171
Acanthamoeba in, 170
Babesia in, 171
Encephalitozoon in, 169-170
Entamoeba in, 170
Theileria in, 171
Toxoplasma, *Neospora*, and *Sarcocystis* in, 163-169
trypanosomes in, 170
- Protozoan polyradiculoneuritis, 434-436
- Pruritus, 100, 102
- Psammomatous meningioma, 359, 360
- Pseudo-Negri bodies, 97, 98
- Pseudomonas mallei*, 151
- Psychosine hypothesis, 220
- Pug
encephalitis in, 111-114, 115
vertebral malformation in, 200
- Pulmonary edema, 37
- Puppy; *see also* Dog
epizootic peroneal and tibial neuropathy in, 446
hypomyelination in, 293
optic nerve hypoplasia in, 79
spongiform degeneration in, 296, 299-300
- Purkinje neurons, 35
in gangliosidosis, 218, 219
- Pyogranulomatous encephalitis, 155
- Pyogranulomatous meningoencephalomyelitis, 118-119
- Pyrexia, 102
- Pyridoxine, 411
poisoning with, 467-468
- ## Q
- Quaking mouse, 294
- ## R
- Rabbit
autoimmune encephalomyelitis in, 18
axonal reaction in, 416
Borna disease in, 149
encephalitozoonosis in, 169, 170
hereditary ataxia of, 299
inherited neuronal dystrophy in, 464
leukodystrophy in, 283
neurofibrillary accumulation in, 313-314
sympathetic neurons of, 413
- Rabies, 95-100
behavior in, 96
clinical signs of, 96
epidemiology of, 99-100
incubation period in, 96, 99
transmission of, 97-98
- Raccoon, 100, 102
- Raccoon-hunting hound, 424
- Radial glial cells, 2
- Radial nerve, 452-453
- Radicals, oxygen-free, 38
- Radiculitis
dorsal root, 25, 26
granulomatous, 436
- Rafoxanide, 266
- Ramified microglia, 21
- Ranvier nodes, 12, 404
- Rat
astrocytomas in, 369
axonal reaction in, 416, 417
Borna disease in, 149
cerebellar cortical abiotrophy in, 301
coronavirus encephalomyelitis in, 149
encephalitozoonosis in, 169
- Rat—cont'd
epidermoid cysts in, 355
hydrocephalus in, 77
hypomyelination in, 293-294
leukemia virus in, 313
meningiomas in, 362
myelocneuropathy in, 321
neuronal aging in, 49-50
neuronal satellites in, 21
oligodendrocyte in, 14
oligodendrogliomas in, 372
pineocytomas in, 379
pituitary tumors in, 384
schwannoma in, 480
scrapie in, 138
spongy degeneration in, 299
thiamine deficiency in, 280
white matter of, 50
- Reactive microglia, 21-22
- Recurrent laryngeal nerve, 448
- Red Danish calf, 315
- Red tail hawk, 454
- Redbone Hound, 424
- Refsum's disease, 214
- Reich granules, 405
- Reindeer-herd dog
glycogenesis in, 232
neuronal abiotrophy in, 306-309
- Remak cells, 406-407
- Remak fibers, 420
- Remyelination, 17-18
- Renal encephalopathy, 208-211
- Renaut bodies, 4, 409
- Reperfusion injury, 237
- rER; *see* Rough endoplasmic reticulum
- Residual body, 214
- Resting microglia, 21
- Reticulosis, 379
in granulomatous meningoencephalomyelitis, 110-111, 112, 113
- Reticulum, endoplasmic
in dog, 411
rough, 415
smooth, 403-404
- Retinol deficiency, 271-272
- Retriever
Golden
cerebellar cortical abiotrophy in, 301
congenital hypomyelinating polyneuropathy in, 441
polymicrogyria in, 74
Labrador; *see* Labrador Retriever
- Retrograde axonal transport, 403
- Retrograde neuronal degeneration, 5
- Rhesus monkey, 244
- Rhinotracheitis, 141
- Rhipicephalus appendiculatus*, 171
- Rhipicephalus sanguineus*, 151
- Rhombencephalitis, 134
- Rhombencephalon, 2

- Riboflavin deficiency, 463-464
 Ricin, 457
 Rickettsial infections, 150-151
 Rift Valley fever virus, 73
 Ringer's solution, 29
 RMSF; *see* Rocky Mountain spotted fever
 Rocky Mountain elk, 139
 Rocky Mountain spotted fever, 150-151
 Rod-shaped microglia, 21-22
 Rodent; *see also* Mouse; Rat
 axonal reaction in, 416
 cerebellar cortical abiotrophy in, 301
 coronavirus encephalomyelitis in, 149
 leukemia virus in, 313
 scrapie in, 138
 thiamine deficiency in, 280
 Rodenticides poisoning, 267
 Romanes stains, 29
 Rosenthal fibers, 282
 Rottweiler
 calcinosis circumscripta in, 204
 leukoencephalomyelopathy of, 285
 neuroaxonal dystrophy in, 315-316
 polyneuropathy in, 445-446
 spinal cord compression in, 200
 spinal muscular atrophy in, 314
 Rough-Coated Collie, 301
 Rough endoplasmic reticulum, 415
 Ruminant; *see also* Cattle; Deer; Goat;
 Sheep
 ancillary procedures in, 48
 hypoglycemia in, 246
 parasitic encephalomyelitis in, 159-161
 polioencephalomalacia in, 277
 Rumpshaker mouse, 294
 Russian knapweed, 263
 Ryegrass staggers, 261, 262
- S**
- St. Bernard
 fibrocartilaginous embolic myelopathy in, 248
 motor neuron disease in, 308
 Salers calf, 230
 Saline fixation, 29
 Saliva, 97, 100
 Salmon poisoning, 151
Salmonella dublin, 156
Salmonella typhimurium, 156, 157
 Salmonellosis, 151
 Salt poisoning, 254-255
 Saluki puppy, 299-300
 Samoyed
 cerebellar cortical abiotrophy in, 301
 hypomyelination in, 291-292
 spongy degeneration in, 296
 Sanfilippo disease, 230
Sarcocystis, 162, 163-169
 Satellite cells, 12, 33
 of peripheral nervous system, 412
 Satellitosis, 3, 16
 neuronal, 39-40, 42, 43
 SBE; *see* Sporadic bovine encephalomyelitis
 Schmidt-Lantermann incisures, 15
 in inherited hypertrophic neuropathy, 438
 myelin artifacts and, 423
 peripheral nervous system and, 404-405
 Wallerian degeneration and, 417
 Schmorl's node, 202, 248-249
 Schnauzer X Beagle, 301
 Schwann cells, 404-407
 in inherited hypertrophic neuropathy, 438-439
 Wallerian degeneration and, 417
 Schwannoma, 473-474
 in cats, 476
 in cow, 480
 in dogs, 475, 476, 478
 in fish, 480
 in rat, 480
 Sciatic nerve, 457
 Sclerosing leukoencephalitis, 110
 Sclerosis
 amyotrophic lateral, 308
 cytoplasmic inclusions in, 7
 multiple, 16, 43
 in old animals, 52
 Scottish Terrier, 282
 Scrapie, 136-139
 Seal, 102
 Second cranial nerve
 degeneration of, 204
 glioblastoma of, 367
 hypoplasia of, 78-79
 infarction of, 249
 Segmental demyelination, 421-422
 Seizure, 244-246
 in canine distemper encephalitis, 105
 in rabies, 96
 Selectins, 40
 Selenium poisoning, 258-261
 Semliki Forest virus, 146
 Senile plaque, 54, 55
 Sensory cell bodies, 410-411
 Sensory ganglia, 410
 Sensory neuropathy, 428-431
 in Dachshund, 443-444
 in Pointer, 442-443
 Sensory perikarya, 411-412
 sER; *see* Smooth endoplasmic reticulum
Setaria, 161-162
 Setter
 Gordon, 301, 304
 Irish
 cerebellar malformations in, 85
 lissencephaly in, 74
 polyneuropathy in, 473
 Seventh cranial nerve, 436
 Shakers, 288
 Sheep; *see also* Lamb
 ancillary procedures in, 48
 Borna disease in, 148
 brain abscess in, 158
 cerebellar cortical abiotrophy in, 301, 304-305
 ceroid-lipofuscinosis in, 234, 236
 copper deficiency in, 273
 enterotoxemia in, 269
 focal symmetrical encephalomalacia in, 270
 gangliosidosis in, 218
 glycogenosis in, 233
 hydranencephaly in, 73
 hypoglycemia in, 246
 hypomyelination in, 288, 289
 hypomyelination in, 287
 ischemic infarct in, 239
 leukodystrophy in, 283
 globoid cell, 221, 458
 louping ill in, 132-133
 meningeal polyarteritis in, 116
 myelopathy in, 324-325
 neuroaxonal dystrophy in, 316-317
 parasitic encephalomyelitis in, 159-161
 poisoning in
 chlorinated hydrocarbon insecticide, 256
 chronic copper, 211
 lead, 251
 organophosphate, 255, 256
 plant, 227-228
 salt, 255
 solanum, 264
 polioencephalomalacia in, 277
 poliomyelomalacia in, 260
 rabies in, 96
 ricketsial disease in, 150
 scrapie in, 136, 137
 spinal cord injury in, 201
 spongiform encephalopathy in, 299
 thiamine deficiency in, 277-280
 toxoplasmosis in, 165
 tremorgenic syndrome in, 261-263
 visna in, 129
 Sheep dog, 316
 Shepherd-cross puppy, 300
Shigella dysenteriae, 268
 Shiverer mouse, 294
 Short-chain fatty acids, 211
 Shorthaired Pointer dog, 442
 Shorthorn cattle
 cerebellar cortical abiotrophy in, 301
 cerebellar malformations in, 85
 glycogenosis in, 232
 hypomyelination in, 290
 Shunts, 208
 Siamese cat, 218, 234
 Siberian Husky, 430, 450

- Siderosis, 7
 Silkie Terrier, 296
 Silky Terrier, 223
 Silver carbonate procedure, 30
 Silver fox, 296
 Silver impregnation technique stain, 29
 Simmental calf, 326-327
 Sip, 138
 Sjögrens syndrome, 430
 Skeletal tumor, 391
 Skunk, 96, 100, 102
 SLE; *see* Systemic lupus erythematosus
 Sly syndrome, 230, 231
 Smooth endoplasmic reticulum, 403-404
 Smooth Fox Terrier, 321
 Snowshoe hare virus, 146
Solanum esuriale, 266
 Solanum poisoning, 264, 265
 Soma, 4
 Somatic motor neuron, 412-413
 Somatofugal atrophy, 8-9
Sophora secundiflora, 263
Sorghum plants, 266
 South Hampshire sheep, 234
 Spaniel
 calcinosis circumscripta in, 204
 cerebellar cortical abiotrophy in, 301
 fucosidosis in, 224, 459-460
 gangliosidosis in, 218
 glycogenosis in, 233
 hypomyelinogenesis in, 291
 neuronal abiotrophy of, 307
 spinal muscular atrophy in, 314
 Spheroids, 8-9
 aging changes in, 50-51
 Sphincter paralysis, 433
 Sphingolipidosis, 218-224, 225
 Sphingomyelinase, 224
 Spina bifida, 88
 Spinal arachnoid cyst, 355
 Spinal cord
 anomaly of, 31
 in arthritis encephalitis syndrome, 129, 130
 chromatolysis in, 6
 compression of, 204-205
 in Wallerian degeneration, 25
 duplication of, 86-87
 in enterovirus encephalomyelitis, 123
 examination of, 27-28
 gray matter in, 2
 in herpesvirus, 146, 147
 in infectious peritonitis, 119
 injuries to, 189-193; *see also* Spinal cord injuries
 malformations of, 86-90
 motor neurons in, 412
 necrosis of, 25
 neurons of, 4
 in polioencephalomyelitis, 119-122
 Spinal cord—cont'd
 tumors of, 386-391
 in visna, 132
 Spinal cord injuries, 189-193
 intervertebral disk disease and, 202-204
 vertebral malformations and, 193-202
 in calves, 201
 in dogs, 198-201
 in horses, 193-198
 multiple cartilaginous exostosis in, 201-202
 in sheep, 201
 Spinal ganglia, 410-411, 412
 Spinal muscular atrophy, 308-309, 314
 Spinal myelinopathy, 325
 Spinal roots, 25
 Spiral bands of Fontana, 407, 423
 Spirochetal infection, 155-156
 Spongiform encephalopathy, 139-141, 299
 Spongioblastoma, 380
 Spongiosis, 3
 Spongy degeneration, 282, 295-300
 Springer Spaniel
 calcinosis circumscripta in, 204
 fucosidosis in, 224, 459-460
 gangliosidosis in, 218
 glycogenosis in, 233
 hypomyelinogenesis in, 291
 Squamous cell carcinoma, 391
 Staggerer gait, 305
 Staggers
 flood plain, 262
 paspalum, 262-263
 phalaris, 7, 263
 ryegrass, 261, 262
 Staining techniques, 29-30, 31, 423
 Standard Poodle, 74
 Stanpandrol, 266
 Static stenosis, 195
 Status spongiosis, 3
 Steatosis, 246
 Stenosis
 of foramen, 199
 lumbosacral, 454
 in myelopathy, 193-198
 Sternberger techniques, 30
 Stockard's paralysis, 308
 Storage disease, lysosomal, 214-237; *see also* Lysosomal storage disease
 Strangles, 158
 Streptococcal meningitis, 157
Streptococcus equi, 158, 437
Streptococcus suis, 157, 159
 Stringhalt, 451-452
 Stroke, 244
Strongylus vulgaris, 159, 161
 Stumbler gait, 305
Stypandra, 266
 Subacute necrotizing encephalomyelopathy, 212
 Subarachnoid hemorrhage, 191
 Subcommissural organ, 33
 Subdural hematoma, 191
 Subependymal cells, 32
 Subependymal plate, 32-33
 Subependymoma, 375
 Subluxation, atlantoaxial, 201
 Substance P, 442
 Sudanophilic leukodystrophy, 281
 Suffolk sheep, 218, 316-317
 Suicide transport, 457
 Sulci, 2
 Suprascapular nerve, 458
 Suprasellar germ cell tumor, 384-385
Swainsona, 227-228
 Swayback, 5, 273-277
 Swedish Gotland pony, 301, 305
 Swedish Lapland reindeer-herd dog
 glycogenosis in, 232
 neuronal abiotrophy in, 306-309
 Sweeny, 458
 Swelling; *see* Edema
 Swine; *see* Pig
 Swine fever, 125-126
 Swiss cattle
 cerebral edema in, 298, 299
 degenerative myeloencephalopathy in, 325
 spinal muscular atrophy in, 315
 sporadic meningoencephalomyelitis of, 141
 Swiss-Webster mouse, 299
 Symmetrical cnccephalomalacia, 269-270
 Symmetrical poliomyelomalacia, 258-261
 Sympathetic neurons, 413, 414
 Syncytial meningioma, 356-360
 Synovial cyst, 198
 Syrian hamster, 294
 Syringomyelia, 77-78
 Systemic lupus erythematosus, 116
 Systems degenerations, 305
- ## T
- Taenia*, 161
 Tail paralysis, 433
 Talfan disease, 123
 Tancytes, 19
 Tapeworm, 161
Taraxacum officinale, 451
 Tay-Sacs disease, 215
 Telencephalon, 2
 Teratocarcinoma, 385
 Teratoid medulloblastoma, 380
 Terminal loops, 405
 Terminology, 503
 Terrier
 astrocytomas in, 364
 ataxia in, 321-322
 atlantoaxial subluxation in, 201

- Terrier—cont'd
 cerebellar cortical abiotrophy in, 301, 302-303
 cerebellar malformations in, 85
 ceroid-lipofuscinosis in, 234
 Gaucher's disease in, 223
 globoid cell leukodystrophy in, 220
 hypoglycemia in, 246
 leukodystrophy in, 282
 lissencephaly in, 74
 myelin ballooning in, 406
 myelopathy in, 321-322
 neuronal abiotrophy of, 306, 307
 sensory neuropathy in, 444
 spongy degeneration in, 296
 tremorgenic syndromes in, 263
 Teschen disease, 123
 Tetany, congenital, 298
 Tetraparesis, 205
 Thalamus, 119, 140
 Thallium poisoning, 466
 Theileria, 171
 Theiler's disease, 124-125
 Thiamine deficiency, 277-280
 Thistle, 263
 Thoracolumbar myelodysplasia, 89
 Thrombotic meningoencephalitis, 143-144
 Thyroxine, 463
 Tibetan Mastiff, 422, 437-439
 Tibetan Terrier, 234
 Tibial neuropathy, 446
 Tick-borne fever, 150-151
 Tiger, 102
 Tight junctions, 36
 Tissue culture, 32
 TME; *see* Thrombotic meningoencephalitis
 Toe
 necrosis of, 442
 paralysis of, 463-464
 Togaviridae, 125, 287
 Toluene, 267
 Torpedoes, 8-9
 Tortured gait, 305
 Toxic plants, 227-228; *see also* Poisoning
 Toxin, diphtheria, 421
Toxocara canis, 162
Toxoplasma, 162, 163-169
 Toxoplasmosis, 434-436
 Toy dogs, 77, 246
Trachyandra divaricata, 236
Trachyandra laxa, 236
 Transient paralysis, 38
 Transitional meningioma, 358, 360
 Transmissible encephalopathy, 139-141
 Transsynaptic neuronal degeneration, 4-5
 Trauma
 to central nervous system, 189-193; *see also* Injury
 to peripheral nervous system, 415, 453-458
 Traumatic feline ischemic myelopathy, 249
 Tremor
 congenital, 290-292, 326
 epidemic, 124
 Tremorgenic syndromes, 261-263
Treponema pallidum, 155
Tribulus terrestris, 266
 Trichlorfon, 84
 Trichoides, 155
 Trigeminal hypertrophic neuropathy, 440
 Trigeminal nerve tumor, 475
 Triton tumor, 478
 True stringhalt, 451
Trypanosoma, 170
 Trypanosomiasis, 431
 Tuberculosis, 151
 Tubuloreticular inclusions, 105, 106
 Tumors
 β -cell, 246
 central nervous system, 351-401
 astroglial, 362-370; *see also* Astrocytoma
 borderline, 352-355
 chordomas in, 386, 387
 choroid plexus, 373-375
 craniopharyngioma in, 385, 386
 cysts in, 352-355
 ependymal, 375, 376
 germ cell, 384-385
 gliomatosis cerebri in, 380
 hamartomas in, 352-355
 lymphoma in, 379
 malformations in, 352-355
 medulloblastomas in, 378
 medullocapithelioma in, 380
 meningeal, 355-362
 metastatic, 391-394
 microgliomatosis in, 380, 381
 neuroectodermal, 378-379
 neuronal, 375-378
 oligodendroglial, 370-373
 pineal, 379
 pituitary gland, 380-384
 polar spongioblastoma in, 380
 skeletal, 391
 spinal cord, 386-391
 peripheral nervous system, 472-481
 in cats, 476
 in cattle, 476-480
 in dogs, 474-476
 in fish, 480
 insulinoma in, 472-473
 lymphoid, 481
 neurofibromas in, 474
 neuronal, 480-481
 paraneoplastic neuropathy in, 472
 perineurioma in, 474
 in rats, 480
 schwannomas in, 473-474
 Turkey
 mycoplasma infections in, 44
 poliomyelomalacia in, 260-261
 riboflavin deficiency in, 463-464
 vitamin E deficiency in, 273
 Tyrosinemia, 211
 Tyzzer's disease, 151
 U
 Ubiquitin, 7
 Unmyelinated axons, 406-407
 Urea cycle, 212
 Uremic encephalopathy, 211
 Urine disease, maple syrup, 211, 297-298
 V
 Vaccine
 hog cholera, 84
 rabies, 99-100
 Vacuoles, 33
 cytoplasmic, 7
 in hepatic encephalopathy, 209
 myelin, 17
 in scrapie, 136-137
 in spongiform encephalopathy, 140
 in sympathetic neurons, 414
 Vampire bat rabies, 97
 van Bogaert-Bertrand spongy degeneration, 295
 Vascular degeneration, 53
 Vascular lesions, 352-353, 354
 Vascular perfusion, 29
 Vasculitis
 adenovirus, 117, 118
 herpesvirus, 146, 147
 lymphocytic, 142
 meningeal, 142
 in thrombotic meningoencephalitis, 143
 Vasogenic edema, 38, 39
 VE; *see* Venezuelan encephalomyelitis
 Venezuelan encephalomyelitis, 144
 Ventral horn
 motor neurons in, 412-413
 necrosis of, 25
 Ventral spinal roots, 25
 Ventriculitis, 119
Veratrum californicum, 71
 Vermineous encephalomyelitis, 159, 160
 Verocay bodies, 474
 Vertebral aplasia, 87-88
 Vertebral dorsal lamina, 199
 Vertebral fractures, 191, 192
 Vertebral malformation, 193-202; *see also* Spinal cord injuries
 Vertebral malformation-malarticulation, 198-199, 200, 201
 Vervet monkey, 468-469
 Vesicular disease, 127-128
 Vestibulocochlear nerve, 436

- Vimentin, 10, 361
 Vincristine neuropathy, 468
 Viral encephalomyelitis, 144-146
 Virino model, 138
 Virus, 44-45
 Akabane, 73, 84
 Bluetongue, 73, 84
 Border disease, 73
 Cache Valley, 73
 in cerebellar malformations, 82-85
 Chuzan, 73
 cytoplasmic inclusions in, 7
 diarrhea, 73, 83-84, 85
 distemper, 31
 encephalomyelitis, 126-127
 encephalomyocarditis, 128
 ependymal cells and, 19
 Epstein-Barr, 143
 feline panleukopenia, 82-83
 herpes; *see* Herpesvirus
 hog cholera vaccine, 84
 LaCrosse, 146
 leukemia, 313
 Main Drain, 146
 neuropathogenic, 44
 Newcastle disease, 117-118
 panleukopenia, 73
 parainfluenza, 117-118
 rabies, 95-100
 Rift Valley fever, 73
 Semliki Forest, 146
 snowshoe hare, 146
 Wesselsbron, 73, 84
 West Nile, 146
 Visna, 129-132
 Vitamin A
 deficiency of, 271-272
 in exencephaly, 69
 Vitamin B₁ deficiency, 277-280
 Vitamin B₆ poisoning, 467-468
 Vitamin E
 deficiency of, 272-273
 degenerative myeloencephalopathy and, 319
 Vomiting and wasting disease, 126-127
 Vulvovaginitis, 141
 VWD; *see* Vomiting and wasting disease
W
 Walker Hound
 epizootic peroneal and tibial neuropathy in, 446
 idiopathic polyradiculoneuritis in, 424
 Wallerian degeneration, 9
 in cervical stenotic myelopathy, 196
 in corticospinal projections, 25, 26
 in ganglioradiculitis, 429, 430
 in peripheral nervous system, 417-420
 in radial nerve, 452-453
 spinal cord in, 25
 in visna, 132
 Wander foal, 240
 Wasted mice syndrome, 313
 Wasting
 chronic, 139
 muscle, 461-462
 Water deprivation, 254, 255
 Water intoxication, 254
 Watershed zones, 237
 WE; *see* Western encephalomyelitis
 Weakness, muscle, 461-462
 Weasel, 102
 Weaver gait, 305
 Weaver syndrome, 325
 Weimaraner, 89, 292-293
 Welsh sheep, 301, 305
 Werdnig-Hoffmann disease, 308
 Wernicke's encephalopathy, 277
 Wesselsbron virus, 73, 84
 West Highland White dog, 220, 263
 West Nile virus, 146
 Western encephalomyelitis, 144
 White-coated dog, 263
 White matter
 aging of, 50-51
 in distemper encephalitis, 105-106, 107
 in globoid cell leukodystrophy, 221
 White matter—cont'd
 in granulomatous meningoencephalomyelitis, 111, 112
 microglia in, 20
 oligodendrocytes in, 12
 in Pug dog encephalitis, 114
 spongy degeneration in, 282, 295-296
 in visna, 131-132
 White snakeroot, 263
 White swine, 301
 White-tailed deer, 158, 159
 Wild birds, 454
 Wildebeest, 277
 Wire Fox Terrier
 cerebellar cortical abiotrophy in, 301
 cerebellar malformations in, 85
 lissencephaly in, 74
 Wobbler disease, 193, 198
 Wobbler mouse, 313
 Wolf, 102
 Woodchuck, 97, 98
X
 X-linked adrenoleukodystrophy, 214
 Xanthoastrocytoma, 364
 Xanthoglioma, 370
 Xylene fixation, 423
Y
 Yellow aging pigment, 7
 Yellow star thistle, 263
 Yorkshire pig
 cerebellar cortical abiotrophy in, 301
 cerebellar disease in, 305
 gangliosidosis in, 218
 spinal muscular atrophy in, 314
 Yorkshire Terrier, 201, 246
Z
 Zebra, 313, 319
 Zebra bodies, 220
 Zellweger's syndrome, 214
 Zitter rat, 294
 Zonulae occludentes, 36